Contemporary Diabetes
Series Editor: Aristidis Veves

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John M. Giurini
Frank W. LoGerfo *Editors*

The Diabetic Foot

Medical and Surgical Management

3rd Edition

Humana Press

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Preface

Although hard to believe, we have already reached the third edition of the book since its first publication in 2002. While we are fully aware that no major breakthroughs have occurred in the management of diabetic foot problems during this period, significant improvements in our knowledge regarding the pathogenesis of diabetic foot problems and in the health care treatment of this condition have taken place. We have therefore tried to include all these developments in this edition. We have no doubt that, given the unabated pandemic of diabetes worldwide, these new developments will be very useful to both researchers and clinical providers involved in the field. As with the previous editions, we have also tried to blend this new knowledge with the time-tested principles of diabetic foot management that are part of the long tradition of the Joslin-Beth Israel Deaconess Foot Center.

It is our hope that the third edition will continue to serve the scientific and clinical community at the same level as the previous two editions have done. In that sense, we are really indebted to the contributors of this edition, the majority of which have contributed to the previous editions. We also wish to thank Humana Press for their support in the project.

Boston, MA, USA

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Part I

Clinical Features and Diagnosis

Principles of Care in the Diabetic Surgical Patient

1

Kenneth Snow

Abstract

The prevalence of diabetes in the USA continues to grow at an alarming rate. While the risk factors for diabetes complications are well defined, many patients are not achieving recognized treatment goals and are at risk of developing complications, including peripheral vascular disease and podiatric problems. There are two major types of diabetes—Type 1 and Type 2. Type 1 diabetes develops into a from of insulin production while Type 2 diabetes develops because of insulin resistance with an inadequate supply of insulin to meet the increased need. When patients with diabetes are admitted to the hospital, they will almost always require insulin therapy. Optimal insulin coverage includes basal (background) insulin in conjunction with insulin. The bolus insulin dose is composed of a prandial (meal) component and a correction dose as needed. For patients eating normally the total daily dose of prandial insulin is approximately equal to the total basal dose. Based on a patient's total daily insulin requirement, one can calculate a correction factor or the amount of blood glucose lowering expected from 1 unit of insulin. Patients with Type 1 diabetes, because of their lack of insulin production, can never have all of their insulin held because of the risk of developing DKA. Adjustments in both the basal and bolus doses are required preoperatively. Patients in the ICU are best managed with an intravenous insulin infusion with dosing based on a validated protocol. Early discharge planning can help avoid delays in discharge due to diabetes-related issues.

Keywords

Type 1 diabetes • Type 2 diabetes • Inpatient • Insulin • Insulin infusion • Ketoacidosis • Basal • Bolus • Prandial • Correction factor • Correction dose • Glargine • Detemir

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Introduction

We are in the midst of a diabetic epidemic. The prevalence of diabetes in the USA as well as worldwide continues to grow at an alarming rate. This growth is due mostly to an increase in the number of cases of Type 2 diabetes related to obesity. According to the CDC in 2010, the most recent year for which we have data, it was estimated that 25.8 million people or about 8.3% of people in the USA had diabetes. The incidence of new cases of diabetes is about 1.9 million cases each year meaning that a more realistic estimate puts the diabetes burden in the USA in 2012 to 28 million people [1]. The complications of diabetes are well known and studies have clearly shown that the risk of complications is dependent on identified risk factors. The risk of retinopathy, nephropathy, and neuropathy, as well as macrovascular complications is influenced by the level of glycemic control as well as other risk factors, such as blood pressure, lipid levels, and smoking [2–4]. Unfortunately, the level of control of these risk factors in the USA is far from optimal [5]. Thus, many patients diagnosed with diabetes and under treatment are at high risk for complications, including peripheral vascular disease due to inadequate glycemic control.

Pathophysiology of Diabetes

Glucose, the predominant source of energy for cell metabolism, is actively transported into cells. This process requires insulin, a hormone produced in beta cells of the pancreas, to bind to an insulin receptor on the cell surface. This binding then leads to phosphorylation of intracellular proteins causing the movement of glucose transport facilitators to move to the cell surface leading to glucose diffusion into the cell [6]. Diabetes mellitus is a condition caused by the inability to efficiently move glucose from the blood into cells. There are two major forms of diabetes—Type 1 diabetes mellitus accounting for approximately 5% of the total cases of diabetes and Type 2 diabetes mellitus accounting for approximately 95% of total cases. In Type 1 DM, there is an absolute deficiency of insulin. Type 1 diabetes was previously referred to as juvenile diabetes because the disease is more likely to occur during childhood with the peak incidence between 8 and 14 years old [7]. In addition to this peak in incidence during the second decade of life, it is now recognized that many cases of Type 1 diabetes will occur in adults with an increased risk during the 6th and 7th decades of life. The incidence of Type 1 diabetes in these later decades actually exceeds the risk in children [8, 9]. In Type 2 diabetes, there is resistance to the action of insulin coupled with a relative deficiency of insulin that is inadequate to meet the increased need [10]. Type 2 diabetes was previously referred to as adult onset diabetes since it is more likely to occur later in life. Since insulin resistance is worsened by obesity, there has been a significant increase in the incidence of Type 2 diabetes. This increase has been seen in all ages of the population, including teenagers. Because Type 1 diabetes does occur in older individuals and because Type 2 is increasing in younger patients, the age of the patient is not a reliable way to identify the type of diabetes present.

Type 1 diabetes is caused by an autoimmune process that selectively destroys the beta cells leading to a reduction in the amount of insulin available. This process can begin years before any clinical manifestations of the disease [10]. As the process continues, the number of beta cells and the amount of insulin produced eventually reaches a level that is inadequate to allow sufficient intracellular transport of glucose. When this level is reached, glucose levels climb significantly. Insulin, however, is not only necessary for the utilization of glucose but is also essential in the regulation of lipolysis. In the absence of insulin, fat breakdown is accelerated with an increased production of ketone bodies. Thus, the production of ketones in a patient with Type 1 diabetes is a sign of insulin deficiency. Untreated, this process accelerates with an increase in the level of ketones. Ketones are acidic and will lead to ketoacidosis if left untreated. Therefore, it is important to remember that a patient with Type 1 diabetes requires some background level of insulin at all times to prevent the production of ketones. The situation is true even in the patient who is not eating. Failure

Table 1.1 Currently available noninsulin diabetes medications

Generic name (product name)	Action
Sulfonylureas	
Glimeperide (Amaryl) Glipizide (Glucotrol) Glyburide (Diabeta) (Micronase)	Stimulate beta call insulin production
Non-SFU secretagogues	
Repaglinide (Prandin) Nateglinide (Starlix)	Stimulate beta call insulin production
Biguanides	
Metformin (Glucophage) (Fortamet)	Decreases hepatic glucose production and improves insulin sensitivity
Alpha-glucosidase inhibitors	
Miglitol (Glyset) Acarbose (Precose)	Delays absorption of carbohydrates from the intestines
Thiazolidinediones	
Pioglitazone (Actos) Rosiglitazone (Avandia)	Improves insulin sensitivity and decreases hepatic glucose production
GLP-1 agonists	
Exenatide (Byetta) (Bydureon) Liraglutide (Victoza)	Increases level of incretin hormone resulting in enhanced insulin sensitivity
DPP-4 inhibitors	
Linagliptin (Tradjenta) Saxagliptin (Onglyza) Sitagliptin (Januvia)	Increases level of incretin hormone resulting in enhanced insulin sensitivity
Bile acid sequestrants	
Colesevelam (Welchol)	Bile acid sequestrant
Dopamine agonists	
Bromocriptine (Cycloset)	Unknown
Fixed combinations	
Glipizide and Metformin (Metaglip) Glyburide and Metformin (Glucovance) Linagliptin and Metformin (Jentadueto) Pioglitazone and Glimeperide (Duetact) Pioglitazone and Metformin (Actoplus met) Repaglinide and Metformin (Prandimet) Rosiglitzone and Glimeperide (Avandaryl) Rosiglitzone and Metformin (Avandamet) Saxagliptin and Metformin (Kombiglyze XR) Sitagliptin and Metformin (Janumet) Sitagliptin and Simvastatin (Juvisync)	See actions of individual components

to provide background insulin can lead to diabetic ketoacidosis (DKA) quite quickly [11].

Patients with Type 2 diabetes are resistant to the action of insulin. This insulin resistance is present for years prior to the development of Type 2 diabetes. In response to this level of insulin resistance, the patient's beta cells increase the amount of insulin that is produced maintaining glucose in a normal range. Over the course of time, these beta cells produce less insulin with a resulting increase in glucose levels. Unlike patients with Type 1 diabetes, patients with Type 2 diabetes still produce some insulin. Even though this amount of insulin may not be adequate to maintain blood glucose levels in the normal range, the amount of insulin produced is almost always adequate to prevent the development of significant ketosis. Therefore, the development of DKA in a patient with Type 2 diabetes is rare [12].

A number of different medications can be used in the treatment of Type 2 diabetes. These medications may improve insulin resistance, increase the amount of available insulin through increasing endogenous production or provide additional exogenous insulin. Frequently, multiple different therapies are combined to take advantage of different modes of action. A list of available medications is provided in Table 1.1.

Diabetes, especially when inadequately controlled, can lead to a number of complications. These include retinopathy, nephropathy, neuropathy, and macrovascular disease. In fact, in the USA, diabetes is the leading cause of blindness in adults under the age of 65 and the leading cause of preventable blindness in adults age 20–74. It is also the leading cause of renal failure and accounts for over 60% of the nontraumatic lower extremity amputations that are performed each year [1]. The goal in treating a patient with diabetes is to control the blood glucose level as well as other risk factors in order to prevent or minimize the risk of developing complications. Despite the recognition of the need for good glycemic control and the availability of numerous medications to improve blood glucose control, many patients are still inadequately treated. Studies have shown that as many 20% of patients are under poor control and 63% are under suboptimal control [5]. Thus, many patients are at an increased risk of complications because of an inadequate treatment of the blood glucose levels.

Peripheral Vascular Disease in Patients with Diabetes

Peripheral vascular disease is a common cause of hospitalization among patients with diabetes. In 2003, there were 873,000 patient discharges with a lower extremity condition (peripheral vascular disease, ulcer/infection, or neuropathy) listed as either the primary or secondary diagnosis among patients with diabetes. This number more than doubled over the previous 20 years [13]. In general, the annual number of diabetes-related hospital discharges with lower extremity nontraumatic amputation as a reported procedure increased from about 33,000 in 1980 to 84,000 in 1997. The number of lower extremity amputation discharges increased significantly in the early 1990s and then leveled off and has been slowly decreasing more recently. This decrease may reflect an improvement in the chronic care of patients with diabetes, a heightened awareness of the seriousness of lower extremity problems in this population as well as improved surgical evaluation and revascularization. In 2006, there were about 66,000 diabetes-related hospital discharges with lower extremity amputation [14].

Considerations for the Inpatient Management of Diabetes

There are a number of issues to consider in treating the patient with diabetes after they are admitted to the hospital. These issues include the differences in pathophysiology between Type 1 and Type 2 diabetes, the wide variety of treatment regimens employed in outpatient treatment as well as the great variability in degree of control among patients with diabetes. While no single set of rules can apply to all patients, utilizing certain fundamental principles can help one develop a reasonable diabetes management plan for the vast majority of patients.

Patients with Type 2 Diabetes

For patients with Type 2 diabetes the major goal of therapy is to achieve good glycemic control. As an outpatient, people with Type 2 diabetes may be on lifestyle therapy only, oral antidiabetes medications, injectable medication or insulin either alone or in combination with any of the above. The first decision that must be made is whether to continue antidiabetes medications during hospitalization in those patients who are on those therapies as an outpatient. For the vast majority of patients, the answer is no and they should be on insulin therapy for the duration of their hospitalization. Most patients who are hospitalized should be switched to insulin because of the many changes that occur in the need for therapy during hospitalization and the greater degree of adjustments that can be made with insulin [15]. There may still be a role for noninsulin therapy in the small number of patients who are admitted for brief hospital stays who will not be in the hospital long enough to have their insulin regimen adjusted and they do not have a contraindication to continuing their present therapy and will be

eating on a regular schedule [16]. If an inpatient is continued on their outpatient regimen, then one must be ready to switch to insulin when it becomes apparent that the patient will not be discharged within 24–48 h. The vast majority of patients with Type 2 diabetes will need insulin therapy when admitted.

Patients with Type 1 Diabetes

For patients with Type 1 diabetes, one must consider the goal of good glycemic control similar to the patient with Type 2 diabetes. In addition, one must keep in mind that patients with Type 1 diabetes produce no insulin. Because of this endogenous insulin deficiency if insulin is withheld for more than a few hours, patients will begin to produce ketones and then develop DKA. Therefore, all patients with Type 1 diabetes admitted to the hospital must continue to have ongoing background insulin. Because they are not able to produce any insulin, they will need additional insulin for any food they eat. For these reasons, under no circumstance a patient with Type 1 diabetes can be treated with sliding scale insulin only.

Hemoglobin A1c Testing

All patients with diabetes should have an hemoglobin A1c (HgbA1c)performed on admission. This test is a measure of the average glycemic control over the prior 2–3 months. Knowing the HgbA1c provides at least three benefits. The first, for those patients who are on insulin therapy, is the ability to know whether the patient's outpatient insulin regimen has been adequate. If the HgbA1c result reflects poor control, then one knows that the patient's outpatient insulin regimen was not adequate and that there is a great likelihood that the regimen will not effectively control the patient during their hospitalization. As such, one should be prepared for the need to adjust the insulin regimen. The second benefit that can be achieved by knowing the HgbA1c is to better anticipate discharge planning needs. For the patient with Type 2 diabetes on oral therapy only who has a very high HgbA1c, it is clear that this therapy was not adequate for the patient and that most likely they will need to be discharged on insulin. Knowing this need early in the hospitalization will provide time to arrange for diabetes teaching in insulin use. In addition, patients already on insulin who need adjustment and intensification in their insulin regimen may also benefit from teaching prior to discharge. Finally, for those patients who are under poor control as an outpatient, consultation with a specialist might be beneficial.

Insulin Management

Insulin Management on a General Floor

There is substantial observational data connecting hyperglycemia during hospitalization to poor outcomes [17, 18]. Yet, there are no prospective randomized controlled trials establishing specific targets for glycemic control in noncritically ill patients. Guidelines based on expert judgment and clinical experience have been published jointly by the American Association of Clinical Endocrinologists and the American Diabetes Association. These guidelines call for premeal blood glucose levels to be less than 140 mg/dL with random blood glucose levels less than 180 mg/dL and to reassess the insulin regimen if the blood glucose level falls below 100 mg/dL. Patients who demonstrate the ability to maintain tight glycemic control as an outpatient may have a tighter range for glucose control compared to those patients who have significant comorbidities who may need less stringent glucose targets [19].

The recommended subcutaneous insulin regimen for noncritically ill patients involves the use of basal and bolus insulin. See Table 1.2 for a list of available insulins. The basal insulin is a long-acting insulin that provides background insulin to maintain good glycemic control overnight and between meals. The bolus insulin is a short-acting insulin that provides insulin coverage for food consumed (prandial dose) as well as insulin to correct for high blood glucose readings (correction dose). This approach to insulin dosing

Table 1.2 Available insulins

	Generic name	Product name
Basal insulin	Detemir Glargine	Levemir Lantus
Intermediate insulin	Insulin NPH	Humulin N Novolin N
Short-acting insulin	Insulin regular	Humulin R Novolin R
Rapid-acting insulin	Insulin Aspart Insulin Glulisine Insulin Lispro	Novolog Apidra Humalog
Premix insulins	Insulin NPH/regular Insulin Aspart Protamine/Insulin Aspart Insulin Lispro Protamine/Insulin Lispro	Humulin 50/50 Humulin 70/30 Novolin 70/30 Novolog mix 70/30 Humalog mix 50/50 Humalog mix 75/25

Premix insulin is a combination of intermediate-acting insulin and short- or rapid-acting insulin. The numbers in the product name reflect the percentage of the intermediate- and short- or rapid-acting insulin, respectively—i.e., Humulin 70/30 is 70% intermediate-acting NPH insulin and 30% short-acting regular insulin.

was shown to be superior to the use of only sliding scale insulin in the Rabbit 2 Trial [20]. There are numerous recommendations for approaching insulin dosing. The most important fact to recognize is that regardless of what starting dose of insulin is used adjustment in the dose will almost always be needed to achieve an adequate level of control. Even patients who are well controlled as an outpatient are likely to require adjustment to their insulin dosing when hospitalized.

For patients not on insulin as an outpatient, the initial dose of basal insulin can be calculated using 0.15–0.2 units/kg of body weight. Thus, the initial dose for a 100 kg patient who needs to start on insulin would be 15–20 units of basal insulin daily. In the Rabbit 2 Trial, an initial basal dose of 0.2 units/kg of body weight was used [20].

For patients who are on basal insulin as an outpatient, the initial basal dose of insulin can simply be a continuation of the outpatient dose. For those patients not on basal insulin but are on the intermediate-acting NPH insulin administered once each day the initial basal dose can also be a continuation of the outpatient dose. If the patient is on twice daily NPH and switching to detemir, then the basal dose can be equal to the outpatient dose. But, if switching from twice daily NPH to glargine, the dose of glargine should be calculated as 80% of the total daily NPH dosage [21, 22].

The total daily prandial insulin requirement, which is the amount of bolus insulin administered prior to meals when the blood sugar is under control, should be approximately equal to the total basal dose. Thus, half of the daily dosage of insulin will be administered as basal insulin and half will be administered as bolus insulin. In the Rabbit 2 Trial, the initial total prandial dose was equal to the initial basal dose [20]. The prandial dose was then divided into three equal doses for each meal. A common misconception is that the amount of bolus insulin required each day is adequate even when it comprises only a small proportion of the total daily insulin dosage. This situation is commonly seen when bolus insulin is ordered by sliding scale with the dose starting at 2 units for a blood glucose level of 150 mg/dL. Frequently, the result is significant hyperglycemia during the day. Fasting blood glucose levels may not be very elevated but a consistent climbing of blood glucose as the day progresses is seen because of inadequate prandial coverage. Providing adequate prandial insulin coverage

will allow good glycemic control with a lower risk for hyperglycemia [20]. Matching up the amount of prandial insulin needed with an appropriate dose is less likely to induce hypoglycemia than providing inadequate prandial insulin followed by an increased amount of basal insulin. With too little prandial insulin patients are far more likely to have elevated blood glucose levels, especially later in the day, followed by an excess of basal insulin putting the patient at risk for hypoglycemia especially while fasting such as during the night. Providing adequate prandial insulin will help avoid these swings in blood glucose. For patients who are not eating the prandial dose of insulin is simply zero.

The correction dose of bolus insulin is used to correct elevated blood glucose levels. The amount of insulin needed is added to the prandial dose of insulin to arrive at the total amount of bolus insulin administered prior to each meal. Clearly, patients who require smaller amounts of insulin each day are more sensitive to the action of insulin and will have a greater correction per unit of insulin compared to a patient who requires a greater amount of insulin each day demonstrating a greater degree of insulin resistance. Again, there are any number of approaches to estimate the correction dose. One such approach is the "rule of 1800" [23]. Originally developed by Paul Davidson in Atlanta as the rule of 1500 when using regular insulin, the rule was modified to take into account the fact that rapid-acting analog insulin will drop blood glucose faster and further. The rule relates the total daily dose of insulin to the amount of blood glucose lowering that will occur with 1 unit of insulin. The rule of 1800 states that taking 1800 and dividing by the total daily dose of insulin will equal the correction factor (the amount of blood glucose lowering that will occur with 1 unit of insulin):

$$\frac{1800}{\text{TDD}} = \text{CF}.$$

For example, a patient who is on a total daily dose of 36 units each day will likely lower their blood glucose by 50 mg/dL for each unit of correction insulin they receive (1800/36). A patient on 72 units total each day will lower their blood glucose only 25 mg/dL for each unit of insulin they receive and would need 2 units to lower their blood glucose 50 mg/dL. For examples of insulin dosing, see Figs. 1.1 and 1.2.

After the patient is on an appropriate insulin regimen, one must reassess whether the dosage is appropriate. The simplest way to assess the adequacy of the basal dose is to see what happens to the blood glucose over time when the patient is not eating. This can be accomplished by observing any change in blood glucose overnight. If the dose of basal insulin is adequate, then the blood glucose should remain relatively flat overnight. If the blood glucose drops significantly, then the dose of basal insulin is too high. Likewise, if the blood glucose climbs overnight, then the dose of basal insulin needs to be increased.

The simplest way to assess the dose of bolus insulin is to assess the change in blood glucose before and then after the dose. This assessment can be done by looking at the change in blood glucose from prebreakfast to the prelaunch reading, from the prelaunch to the presupper reading and then from presupper to the nighttime blood glucose reading. If the bolus dose of insulin is adequate, then the prandial dose should be enough to cover the food that is eaten. Thus, if the blood glucose prior to the meal is good and no correction dose is given, then the next reading should also be in the desired range. If the blood glucose climbs, then the prandial dose is inadequate. If the premeal blood glucose level is elevated, then the bolus dose (composed of the prandial insulin and the correction dose) should cover the food eaten and correct the blood glucose so that the next reading should be within the desired range. If the next reading is still above goal, then the bolus dose is not adequate and the prandial and correction needs to be increased. An inadequate correction dose should be fixed by increasing the bolus insulin and not by increasing the basal dose.

Insulin Pumps

Some patients admitted to the hospital may be treating their diabetes as an outpatient utilizing

	Before breakfast, lunch and supper		Before bedtime	
Blood glucose (mg/dl)	Insulin dose (units)	Explanation	Insulin dose (units)	Explanation
< 70	Treat	Treat hypoglycemia	Treat	Treat hypoglycemia
71-100	10	Prandial = 12 Correction = -2	0	Prandial = 0 Correction = 0
101-150	12	Prandial insulin dose	0	Prandial = 0 Correction = 0
151-200	14	Prandial = 12 Correction = 2	2	Prandial = 0 Correction = 2
201-250	16	Prandial = 12 Correction = 4	4	Prandial = 0 Correction = 4
250-300	18	Prandial = 12 Correction = 6	6	Prandial = 0 Correction = 6
301-350	20	Prandial = 12 Correction = 8	8	Prandial = 0 Correction = 8
351-400	22	Prandial = 12 Correction = 10	10	Prandial = 0 Correction = 10
> 400	Notify MD		Notify MD	

Fig. 1.1 Building an insulin regimen: 50-year-old man with 10-year history of Type 2 diabetes is admitted for a right foot cellulitis and IV antibiotic therapy. As an outpatient he is on 36 units of glargine insulin before bed along with metformin and glimeperide. His Hgb A1c = 7.9%. His appetite is fine. You plan to stop his oral agents and continue with insulin therapy to control his blood glucose. You opt to continue his glargine at 36 units qHS. You now need to calculate his short-acting bolus insulin dosing. Based on his basal dose of 36 units you estimate his initial prandial insulin requirement to also be 36 units which you order as 12 units before each meal. Since he is not eating at bedtime, he needs no prandial dose at bedtime. His total daily dose of insulin is 72 units. Utilizing the rule of 1800 you estimate his correction factor to be 25 (1800/72 = 25). In other words, 1 unit of insulin will lower his blood glucose by 25 mg/dL and 2 units should lower his blood glucose by 50 mg/dL. This correction is added to the prandial dose as needed

an insulin pump. The first decision that must be made is whether the patient is able to continue on their insulin pump during their hospitalization. If the answer is no, then an alternative insulin regimen must be prescribed. In order to make an appropriate decision regarding the use of insulin pumps, one must understand the basics of how an insulin pump works and what it will and will not do. An insulin pump utilizes only short-acting insulin. Small amounts of insulin are administered by the pump continuously via a small cannula that the patient places subcutaneously. This insulin acts as the background or basal insulin. The rate of insulin delivery is programmed into the pump by the user. Because the programmed rate of insulin delivery can be different at different times of the day, there is a greater ability to match the supply of basal insulin with the demand. Additional insulin is administered from the pump whenever the patient eats. This insulin bolus or prandial insulin is usually based upon the amount of carbohydrate which will be consumed. The patient needs to assess the amount of carbohydrate that they will eat, enter that information into the pump which then calculates the appropriate amount of insulin for that meal. The patient then instructs the pump to administer the insulin. In addition, the patient can instruct the pump to deliver a bolus of insulin to correct for high blood glucose levels, either in conjunction with or separate from a prandial dose of insulin, based on a previously programmed correction factor. Thus, while the insulin is administered by the pump, the amount of insulin to be delivered is determined based on the amount of carbohydrate that is to be consumed and the level of blood glucose. Both of these factors must be assessed by the patient and programmed into the pump and

	Before breakfast, lunch and supper		Before bedtime	
Blood glucose (mg/dl)	Insulin dose (units) Treat	Explanation	Insulin dose (units) Treat	Explanation
< 70		Treat hypoglycemia		Treat hypoglycemia
71-100	5	Prandial = 6 Correction = -1	0	Prandial = 0 Correction = 0
101-150	6	Prandial insulin dose	0	Prandial = 0 Correction = 0
151-200	7	Prandial = 6 Correction = 1	1	Prandial = 0 Correction = 1
201-250	8	Prandial = 6 Correction = 2	2	Prandial = 0 Correction = 2
250-300	9	Prandial = 6 Correction = 3	3	Prandial = 0 Correction = 3
301-350	10	Prandial = 6 Correction = 4	4	Prandial = 0 Correction = 4
351-400	11	Prandial = 6 Correction = 5	5	Prandial = 0 Correction = 5
> 400	Notify MD		Notify MD	

Fig. 1.2 Building an insulin regimen: 50-year-old man with 8-year history of Type 2 diabetes is admitted for a right foot cellulitis and IV antibiotic therapy. As an outpatient he is on metformin, glyburide, and pioglitazone. His Hgb A1c = 8.2%. His appetite is fine. You plan to stop his oral agents and start insulin therapy to control his blood glucose. His weight is 90 kg. You opt to start detemir insulin at 18 units (0.2 × 90 kg) qHS. You now need to calculate his short acting bolus insulin dosing. Based on his basal dose of 18 units you estimate his initial prandial insulin requirement to also be 18 units which you order as 6 units before each meal. Since he is not eating at bedtime, he needs no prandial dose at bedtime. His total daily dose of insulin is 36 units. Utilizing the rule of 1800 you estimate his correction factor to be 50 (1800/36 = 50). In other words, 1 unit of insulin will lower his blood glucose by 50 mg/dL. This correction is added to the prandial dose as needed

then the patient must instruct the pump to deliver the dose. In addition, insulin pumps also have safety features which will trigger alarms for various problems, such as the pump running low on insulin, a lack of insulin delivery or if the pump disconnects from the patient. Therefore, for patients to remain on the pump they must be well enough to calculate their insulin needs, program that information into the pump, and be able to troubleshoot any alarms. If there is any question about a patient's ability to perform all these tasks, then the pump should be discontinued and subcutaneous insulin started. In switching somebody from an insulin pump to subcutaneous insulin, the amount of basal insulin that is required is usually slightly greater when administered as a subcutaneous injection of insulin rather than from the pump. As an initial dose, one can substitute the amount of basal insulin administered over 24 h with an equal dose of a long-acting basal insulin (glargine or detemir) administered subcutaneous. The bolus insulin can be calculated as previously described. These doses can then be adjusted as needed.

Intensive Care Unit Insulin Management

It is well recognized that the degree of glycemic control in critically ill patients does correlate with patient mortality. Numerous studies have evaluated the question of glycemic control and patient outcomes in the intensive care unit (ICU) setting [18, 19, 24]. Yet these studies are limited since they are observational studies and do not

identify causation. The fundamental question is whether improved glycemic control will lead to improved patient outcomes. Van den Berghe evaluated over 1,500 patients in a surgical ICU in a prospective randomized controlled trial [25]. Conventional therapy required starting insulin when the blood glucose exceeded 215 mg/dL and the intensively treated group started insulin when the blood glucose exceeded 110 mg/dL. The goal for blood glucose control in the intensively treated group was between 80 and 110 mg/dL. The mean morning blood glucose in the conventional group was 153 compared to 103 in the intensively treated group. Results demonstrated a dramatic decrease in mortality as well as sepsis, the need for dialysis and the need for blood transfusion.

The Nice-Sugar (The Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation) trial was designed to see if even tighter glycemic control would prove of further benefit [26]. Over 6,100 patients were randomized to receive either conventional insulin treatment with the goal of achieving a blood glucose level of under 180 mg/dL vs. intensive insulin treatment with a goal of achieving a blood glucose level between 81 and 108 mg/dL. The study was performed utilizing both surgical as well as medical patients in the ICU. The mean time-weighted blood glucose level achieved in the conventional treated group was 144 mg/dL compared to 115 mg/dL in the intensively treated group. Patients in the intensively treated group had an increased mortality with an odds ratio of 1.14. This increased mortality was seen in both surgical and medical patients. While there was a trend for an even worse mortality in the intensively treated surgical patients compared to intensively treated medical patients, this difference was not statistically significant.

Based on this data as well as numerous other studies, the American Association of Clinical Endocrinologists recommends that insulin therapy should be initiated for persistent hyperglycemia of at most 180 mg/dL. Once insulin therapy is started the blood glucose goal is between 140 and 180 mg/dL. In critically ill patients, intravenous insulin infusion utilizing a validated insulin infusion protocol is the preferred method of administration [19]. Numerous IV insulin infusion protocols are available. A sample protocol is shown in Fig. 1.3. This protocol takes into account not only the level of blood glucose, but also the rate of change.

Perioperative Insulin Management

The goal of insulin management during the hospital stay is to maintain appropriate glycemic control with the avoidance of hypoglycemia. Because the patient is not able to recognize and complain of hypoglycemic symptoms during the perioperative period the issue of safety is heightened. In addition, since the perioperative period is relatively short, the need for tight glycemic control is less critical. Maintaining the blood glucose between 140 and 180 mg/dL during the perioperative period should meet both of these requirements. Patients who are on an IV insulin infusion prior to surgery should be continued on this therapy through the perioperative period. The IV infusion allows the greatest degree of control over the blood glucose as well as a high degree of safety. Blood glucose should be monitored every hour and the rate of insulin infusion should be adjusted based upon an accepted algorithm, such as the one outlined in Fig. 1.3.

Patients who are on subcutaneous insulin prior to surgery can be maintained on a subcutaneous insulin regimen but with some modifications. Patients are frequently on basal insulin, such as glargine or detemir. These insulins provide basal or background insulin coverage. Therefore, when the patient is NPO and on an appropriate dose of basal insulin, one would expect that no adjustment in the dose is needed. But, because of the variability in blood glucose levels from day to day even an appropriate dose of basal insulin can occasionally induce hypoglycemia. A hypoglycemic event, either because of its severity or because of the need for oral glucose, can lead to either delay or cancelation of planned surgery. As such, the preferred approach is to decrease the dose of basal insulin prior to surgery by 20% thus affording a greater degree of assurance of avoiding a hypoglycemic event [27]. High blood

Insulin Infusion Algorithm for Critically Ill Intraoperative and Medical ICU Patients (Target BG 140-180 mg/dl)

Insulin dose adjustments using this algorithm do not replace sound medical judgment.

<100	Hold drip and give ½ - 1 amp 50% glucose and check BG every 30 minutes until >140 mg/dl and then re-initiate drip at 50% previous rate							
Current BG level (mg/dl)	**Previous Blood Glucose (mg/dl)**							
	<100	**100-140**	**141-180**	**181-200**	**201-250**	**251-300**	**301-400**	**>400**
101-140	↓ rate by 1unit/hr	↓ rate by 25% or 0.5 units/hr*		↓ rate by 50% or 2 units/hr*			↓ rate by 75% or 2 units/hr*	
141-180	No Change				↓ rate by 50% or 2 units/hr*			
181-200	↑ rate by 1 unit/hr	↑ rate by 0.5 units/hr		↑ rate by 25% or 1 unit/hr*	No Change	↓ rate by 25% or 2 units/hr*		
201-250	↑ rate by 25% or 2 units/hr*			↑ rate by 25% or 1 unit/hr*			↑ rate by 1 unit/hr	No Change
251-300	↑rate by 33% or 2.5 units/hr*		↑ rate by 25% or 1.5 units/hr*	↑ rate by 25% or 1 unit/hr*	↑ rate by 1 unit/hr	↑ rate by 1.5 units/hr	↑ rate by 25% or 2 units/hr*	No Change
301-400	↑ rate by 40% or 3 units/hr*							
>400	↑ rate by 50% or 4 units/hr*							

- ***Whichever is greater change**

↓

This algorithm assumes hourly BG checks during insulin dose titration.

↓

- If BG in desirable range (140-180 mg/dl) for 4 hours, decrease frequency of BG checks to every 2 hours while BG stays in target.
- If experiencing unexplained hypoglycemia or hyperglycemia, investigate and correct causative factors.
- If there is any significant change in glycemic source (i.e., parenteral, enteral or oral intake), expect to make insulin adjustment.

↓

Common reasons to discontinue insulin infusion:

- Patient tolerating at least 50% of normal oral intake or enteral feedings
- Clinically appropriate to transfer patient to a unit that does not do insulin infusions
- Patient on stable regimen of TPN with most of insulin already in TPN solution

↓

Two hours before discontinuing insulin infusion, initiate alternative glycemic management:

- For patients with type 1 diabetes or those with type 2 diabetes previously controlled on insulin: If NPO, initiate basal subcutaneous insulin (glargine, detemir or NPH) at 80% of the insulin administered over the previous 24 hours by insulin infusion. If the patient is taking more than 50% of usual oral or enteral intake, give 50% of insulin dose as basal insulin based on previous 24 hours of insulin infused or 0.25 units/kg and initiate pre-meal bolus and correction dose to maintain BG in target. Another alternative is to resume pre-hospital insulin regimen. Insulin pump patients can resume pump use based on hospital policy.
- For patients with type 2 diabetes previously treated with oral antidiabetes agents: If patient had good diabetes control previous to hospitalization, a return to oral agent therapy may be considered based on postoperative clinical status; if pre-hospital control was inadequate, plan for discharge on subcutaneous insulin.

Fig. 1.3 Intravenous insulin infusion protocol. (Copyright 2009 by Joslin Diabetes Center. All rights reserved. Excerpted with permission from Joslin's Guideline for Inpatient Management of Surgical and ICU Patients with Diabetes. Refer to Joslin's Web site (www.joslin.org) for updates to its Clinical Guidelines)

glucose levels on the morning of surgery can be corrected through the use of a correction dose of short-acting insulin. The bolus dose of insulin comprises the prandial insulin component as well as the correction component as discussed previously. Since the patient is NPO, the prandial dose is zero. The correction dose is not affected. Thus, the dose of bolus insulin includes only the correction dose. This dose should be the same as the prebed insulin scale since the prandial dose of insulin at bedtime is zero. Therefore, the prebed insulin scale can be used when the patient is NPO (see Figs. 1.1 and 1.2).

For patients who are not on basal insulin but instead are treated with NPH insulin, adjustments are also needed. In theory, a dose of NPH given before supper or bedtime would not need to be reduced since the duration of action of the NPH is short enough that most of the action of the insulin is gone by morning. Even though the patient is NPO overnight, their food intake during the night is no different than it is on other nights—people are routinely NPO overnight only to eat again in the morning. Yet, the dose of NPH is often decreased by 20% because of the variability of blood glucose and the desire to avoid hypoglycemia as previously described regarding the use of basal insulin [25]. The morning dose of NPH needs to be decreased since NPH insulin does have a peak and will induce hypoglycemia in a patient who is not eating. The dose needs to be decreased by at least 50% [28]. One must remember that patients with Type 1 diabetes need continuous background insulin even when not eating to avoid the production of ketones and the risk of developing DKA. Therefore, one must never completely hold the dose of the morning NPH and use only short-acting insulin in a patient with Type 1 diabetes. The adjustment to the dose of bolus insulin is identical to that for patients who are on basal–bolus insulin regimen. The prandial dose of insulin is zero and only the correction dose of bolus insulin is used.

For patients who are on a premixed insulin, one should calculate the amount of NPH insulin and the amount of short-acting insulin in each dose. One should then proceed as if the patient were on NPH insulin along with short-acting insulin. The dose of NPH insulin should be adjusted as noted above and administered. Again, the dose of short-acting insulin should be held since the patient is NPO and correction scale should be ordered in case the blood glucose is unacceptably high and needs to be adjusted. A summary of insulin adjustment in the perioperative period can be found in Table 1.3.

Table 1.3 Adjustment to insulin preoperatively

Insulin type	Insulin	Adjustment
Basal	Detemir (Levemir) Glargine (Lantus)	20% reduction
Intermediate	NPH (Humulin N) (Novolin N)	20% reduction the night before surgery 50% reduction the morning of surgery
Short-/rapid-acting	Aspart (Novolog) Glulisine (Apidra) Lispro (Humalog) Regular (Humulin R) (Novolin R)	Prandial dose = 0 Correction dose unchanged (can use HS scale)

Discharge Planning

Prior to discharge, one must assess whether the patient will need additional education or skill training in order to be discharged safely. The earlier discharge planning begins the less likelihood that a patient's discharge will be delayed due to an issue with their diabetes. This situation is common for patients who were not on insulin at the time of their admission but will need to be discharged on insulin either because their diabetes was under poor control prior to hospitalization and insulin therapy was needed or because the patient's illness has exacerbated their glycemic control and insulin will be needed at least temporarily. Regardless of the cause for insulin therapy, once it becomes clear that the patient will need insulin therapy after discharge appropriate diabetes education should be instituted. Another common situation when education will be needed is the patients who were unaware that they had diabetes prior to hospitalization and the diagnosis is made during their hospitalization.

The goal of diabetes teaching during hospitalization is to provide the patients with the basic skills necessary to be safely discharged. Appropriate follow-up should be arranged with either their primary care physician or an endocrinologist as well as with a certified diabetes educator for further diabetes education.

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Epidemiology and Health Care Cost of Diabetic Foot Problems

2

Jeremy J. Cook and Donald C. Simonson

Abstract

In 1992, Zimmet first referred to the "epidemic of diabetes," noting that its costs both in terms of economic burden and human suffering are rising at an alarming rate (Zimmet, Diabetes Care. 1992;15(2):232–52). The global prevalence of diabetes mellitus has been projected to nearly double from a baseline of 2.8% in 2000 to 4.4% by 2030, affecting over 350 million individuals (Wild et al. Diabetes Care. 2004;27(5):1047–53). In the decade beginning in 1997, the prevalence of diabetes in the USA has increased by 48% (http://apps.nccd.cdc.gov/DDTSTRS/default.aspx) (Fig. 2.1). Lower extremity morbidity contributes substantially to the toll diabetes takes on the individual and the health care system. This chapter focuses on the epidemiologic aspects of risk factors and complications in the diabetic lower extremity, particularly as they relate to the outcome of amputation. Included in the discussion is the influence of demographic factors, such as gender, age, race, and socioeconomic considerations, as well as the cost to the health care system of lower extremity disease in diabetes.

Keywords

Diabetic peripheral neuropathy • Peripheral vascular disease • Diabetic ulcer pathway • Musculoskeletal deformities • Ulcerations • Amputations • Lower extremity disease • Diabetic limb

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Introduction

In 1992, Zimmet first referred to the "epidemic of diabetes," noting that its costs both in terms of economic burden and human suffering are rising at an alarming rate [1]. The global prevalence of diabetes mellitus has been projected to nearly double from a baseline of 2.8% in 2000 to 4.4%

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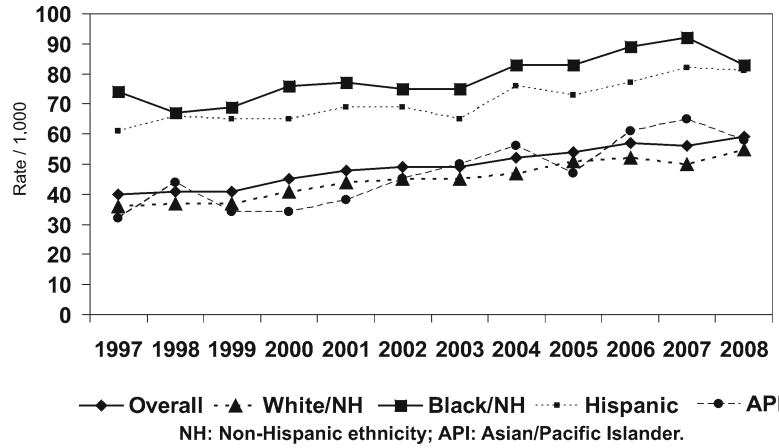

Fig. 2.1 Diabetes prevalence [3]

by 2030, affecting over 350 million individuals [2]. In the decade beginning in 1997, the prevalence of diabetes in the USA has increased by 48% [3] (Fig. 2.1). Lower extremity morbidity contributes substantially to the toll diabetes takes on the individual and the health care system. This chapter focuses on the epidemiologic aspects of risk factors and complications in the diabetic lower extremity, particularly as they relate to the outcome of amputation. Included in the discussion is the influence of demographic factors, such as gender, age, race, and socioeconomic considerations, as well as the cost to the health care system of lower extremity disease (LED) in diabetes.

Epidemiology of Individual Risk Factors

The individual systems at risk that predispose an individual to ulceration are covered in greater detail throughout this textbook. In this chapter, a brief introduction to these risk factors is presented as they relate to the epidemiology of the at-risk foot.

Neuropathy

A frequently encountered complication of diabetes mellitus is neuropathy. Diabetic peripheral neuropathy (DPN) is an impairment of normal activities of the nerves throughout the body and can alter autonomic, motor, and sensory functions [4]. The reported prevalence of DPN ranges from 16% to as high as 66% [5–9]. According to a study utilizing National Health and Nutrition Examination Survey (NHANES) data of 2,873 noninstitutionalized adults aged 40 years and older, the prevalence of peripheral neuropathy in people with diabetes ($n=419$) was 28.5% (95% CI 22.0–35.1). The prevalence of peripheral neuropathy in people with diabetes was almost twice as high as in those without diabetes (14.8% (95% CI 12.8–16.8)) [10]. Another study utilizing NHANES data found that the incidence of peripheral neuropathy was higher in people with undiagnosed (16.6%) and diagnosed (19.4%) diabetes when compared to people without diabetes or with impaired fasting glucose levels between 100 and 125 mg/dL [11]. In the mid-1990s, the annual incidence of peripheral neuropathy was nearly equivalent between genders, but more recent data have shown a growing gap with male incidence climbing [12] (Fig. 2.2).

Although many manifestations of neuropathy may go unrecognized by the patient, autonomic neuropathy is perhaps the most overlooked in the diabetic limb. In addition to contributing to impaired vasoregulation, it also may result in changes to the texture and turgor of the skin, such as dryness and fissuring. Dysregulation of local

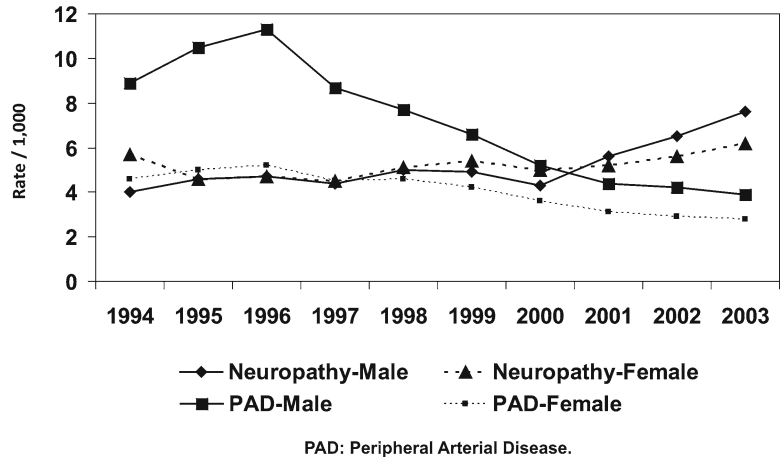

Fig. 2.2 Rates of neuropathy and PAD by gender according to hospital discharges [12]

perspiration may contribute to increased moisture and increase the risk of fungal infections. With increased stiffness within the skin, areas of friction are less flexible and hyperkeratotic lesions may develop. Untreated, these lesions may progress with respect to thickness and induration, and exert increased pressure on deep tissues with resultant ulceration [13, 14].

Another form of neuropathy that influences the diabetic limb is reduced motor function. Frequently, this targets the intrinsic musculature of the foot resulting in joint instability. As innervation decreases, muscle wasting is observed. Over time, these imbalances lead to flexible deformities that become progressively more rigid. Rigid deformities are subject to greater pressure and predispose patients to ulcer formation [4].

Perhaps the most commonly recognized form of neuropathy among patients with diabetes is sensory neuropathy, resulting in the loss of sensation beginning in the most distal part of the extremity. This may manifest as an inability to detect temperature changes, vibration, proprioception, pressure, and, most seriously, pain. Some patients have a form of painful sensory neuropathy that includes symptoms, such as burning and tingling, known as paresthesias. This also contributes to the risk of ulcer formation as they may be unaware of pain associated with smaller injuries because of the persistent neuropathic pain [4]. The prevalence of painful DPN is difficult to truly measure and define. NHANES estimated that 10.9% of adults with diabetes suffered from symptomatic DPN. Symptomatic DPN was defined as painful sensations, tingling, numbness, or loss of feeling. A population-based study through the Mayo clinic found that 20% of their diabetic cohort had painful DPN [5]. In the UK, the prevalence of chronic painful DPN was found to be 16.2% [15] and the incidence, through a UK research database, was 15.3/100,000 patient-years (95% CI 14.9–15.7) [16]. Although there is a lack of high-quality data available from a population health perspective, the prevalence of DPN is believed to increase with the duration of diabetes, poor glucose control, age, and smoking [7, 17, 18]. There is significant variability in the prevalence of DPN reported in the literature. This is most likely attributable to differences among each study's population, geographic location, time period evaluated, definition of neuropathy, method of diagnosis, and source of data (i.e., patient self-report, billing codes, medical records, physician reports).

Peripheral Vascular Disease

Consequences of the compromised vascular system in diabetes can be among the most devastating complications. Both macro- and microvascular diseases are believed to contribute to the

consequences of peripheral vascular disease, resulting in the inability of the dysvascular or ischemic limb to heal itself properly. Small injuries may progress to larger wounds because of reduced healing capacity. Delivery of systemic antibiotics can be compromised and leave infections uncontrolled. Among patients with diabetes, all blood vessels regardless of size and function are affected [19]. The prevalence of peripheral arterial disease (PAD) is higher in people with diabetes compared to the general US population. NHANES found that the prevalence of PAD was 4.5% (95% CI 3.4–5.6) in the general population but increased to 9.5% (95% CI 5.5–13.4) in persons with diabetes [10]. Figure 2.2 also illustrates that the largest disparity between genders was in 1996, and since that time the gap has reduced substantially with near equality of the rate per 1,000 diabetic patients in 2003 [12]. Studies have shown that peripheral vascular disease develops at a younger age among patients with diabetes as compared to the general population [20]. In one large population-based study, over half of diabetic subjects were found to have absent pedal pulses, a common sign of impaired vascular function [20]. Another study found that in patients with nonpalpable pulses, the relative risk of ulceration was 4.72 (95% CI 3.28, 6.78) as compared to a normal exam with all four pulses palpable [21]. Ankle-brachial index (ABI), despite recognized limitations in the diabetic population, has also been used in diabetic screening. In patients with an ABI <0.90, the relative risk has been reported to be 1.25 (95% CI 1.05, 1.47) for developing an ulcer vs. diabetic patients with a normal ABI [22].

Musculoskeletal Deformity

Musculoskeletal deformities play an important role in the diabetic ulcer pathway. The presence or absence of a deformity, such as a hammertoe or bunion, predisposes the structures to increased pressure and friction. As noted above, motor neuropathy may contribute to such deformities, but other diabetes-associated complications such as glycation of collagen have also been indicted [23–25]. In a population-based study of a nationally representative sample, the prevalence of LED has been found to be significantly higher in those with diabetes (30.2% (95% CI 22.1–35.1)) compared to those without diabetes (18.7% (95% CI 15.9–21.4)) in the USA [10].

The prevalence of foot deformity in people with diabetes is not known, but the presence of foot deformity has been shown to increase the risk of developing a foot ulcer. One study found that 63% of patients who developed an ulcer had a fixed deformity beforehand [26]. In one large population-based study of diabetes, the relative risk of ulcer occurrence was 2.56 (95% CI 2.04, 3.22) among patients with deformities as compared to individuals with no or few deformities [21]. Boyko et al. identified the presence of an abnormally shaped foot as carrying a relative risk of 1.93 (95% CI 1.07, 3.48) for ulceration [22]. A study by Mason and associates found that patients with diabetes had similar proportions of deformities to rheumatoid arthritis patients [27].

Metabolic and Systemic Risk Factors

In addition to specific risk factors noted above, the prevalence of LED is also increased among patients with several modifiable systemic risk factors. Cross-sectional and cohort studies have established that better glycemic control is associated with reduced risk of lower extremity amputation (LEA), but this has been difficult to demonstrate in randomized trials [28, 29]. The American Diabetes Association recommends that many complications, including LED, may be reduced by maintaining HbA1c <7.0%, blood pressure <130/80, HDL cholesterol >50 mg/dL, normal weight (BMI 18.5–25 kg/m [2]), and not smoking. Using data from 1999 to 2004 NHANES, Dorsey et al. reported that diabetic patients with LED were less likely to have met HbA1c (39.5% vs. 53.5%) and HDL cholesterol targets (29.7% vs. 41.1%) than patients without LED. Among non-Hispanic (NH) Blacks with LED, it was also noted that systolic and diastolic blood pressure was significantly less likely to be controlled than among non-Hispanic Whites [30].

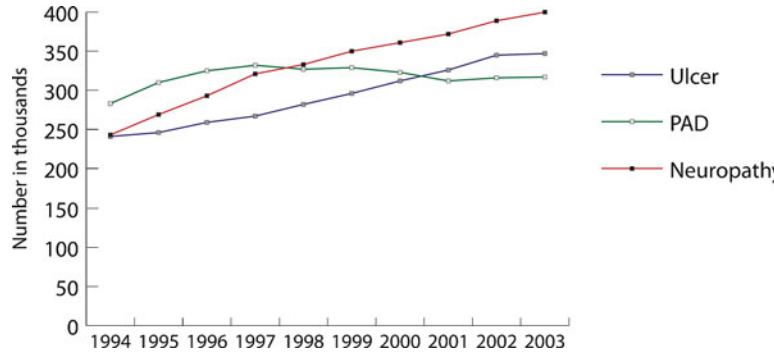

Fig. 2.3 Hospital discharges for lower extremity conditions (PAD, Neuropathy, and Ulcer with associated pathology) with a diagnosis of diabetes [12]

The Perfect Storm

Thus far, the presence of individual risk factors leading to ulceration has been described, but this fails to capture the interaction of these risk factors in the clinical setting. Reiber and colleagues have proposed a widely accepted causal pathway, which incorporates the relationships between risk factors and ulcerations [26]. They advocate that the singular presence of individual risk factors represents a component but not a sufficient cause for acute ulceration. Rather, they found that the presence of two or more risk factors increased the risk of ulceration between 35 and 78% depending on the component risk factors. Furthermore, they noted that a "clinical triad" comprising neuropathy, minor foot trauma, and foot deformity was present in more than 63% of cohort patients who developed an ulcer. Peripheral neuropathy as represented by loss of protective threshold was evident in 78% of ulcer pathways, while peripheral vascular disease was a component cause in 35% of the pathways. Foot deformities were identified as a component cause in 63% of ulcer pathways [26].

Ulcerations

Schaper defined a diabetic foot ulcer as any wound below the ankle with disruption of the integument, including gangrenous tissue [31]. The annual incidence of diabetic ulceration has been reported to be between 1.9 and 4.1% in population-based studies of at least 1,000 subjects [21, 32, 33]. One study noted that the prevalence of foot ulcerations was 7.7% among diabetic as compared to 2.8% among nondiabetic individuals [10]. Singh and associates reported that the lifetime risk of developing an ulcer among diabetic patients ranges between 15 and 25% [34]. Over a decade, the number of discharges in the USA related to an ulcer increased from 241,000 in 1994 to 347,000 in 2003 [12] (Fig. 2.3). Healing wounds can be difficult, and the longer the wound is open the greater the likelihood of a complication, such as infection. Even if a wound heals, the risk of recurrence is high. Apelqvist et al. reported that 70% of patients with diabetic foot ulcers will suffer reulceration within 5 years [35]. Ulcer recurrence rates have been found to range from 28% at 12 months [36] to 100% at 40 months [37].

In a cohort of 370 patients presenting with diabetic foot ulcers, only 62.4% primarily healed all wounds. Of those patients who healed their wounds, 40.3% developed a subsequent wound after a median of 126 (14–903) days. Using Kaplan–Meier survival analysis, the authors found that the greatest period of risk for reulceration was within the first 50 days after healing. Moreover, they noted that the proportion of patients that had avoided early reulceration and remained ulcer free was 63 and 55% at 12 and 24 months, respectively [38]. Figure 2.4 shows the results of five prospective studies on primary healing, amputation, and death in patients with a diabetic foot ulcer [39–42].

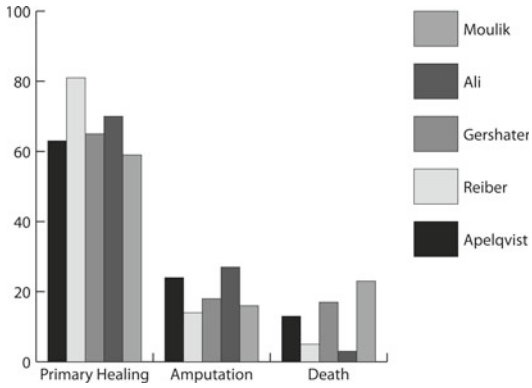

Fig. 2.4 Prospective studies on primary healing, amputation, and death in patients with a diabetic foot ulcer [39–42]

Table 2.1 Clinical outcomes of diabetic foot ulcers by etiology [40, 41]

Study type of ulcer	Primary healing (%)	Amputation (%)	Death (%)
Gershater ($n=2,480$)			
Neuropathic	79.4	9.5	11.1
Neuroischemic	44.4	30.1	25.5
Moulik ($n=157$)			
Neuropathic	65.4	9.6	25
Neuroischemic	59	23	18
Ischemic	29	25	46

Frequently, the hazardous perceptions of diabetic foot ulcers are attributed to their association with infection and amputation. Research in the past decade has indicated that the presence of an ulcer itself is associated with mortality risks. One such study found that the overall 5-year mortality rate was 44% following ulceration [41]. Even after removing patients who had gone on to amputation, the mortality rate was 43% after 5 years. Another important consideration raised by Moulik et al. was the influence of ulcer etiology on outcomes. Specifically, it was found that individuals with ischemic ulcers had a higher 5-year mortality rate and shorter median time to death than purely neuropathic and mixed neuroischemic ulcers. Similarly, the 5-year amputation rate was significantly lower in patients with a purely neuropathic ulcer than either group with an ischemic etiology [41]. Gershater et al. further explored the impact of ulcer etiology on outcome, with the results of both studies noted in Table 2.1 [40, 41].

As evidenced in Table 2.1 and Fig. 2.4, the development of a foot ulcer is a major risk factor for LEAs [43]. In fact, it has been proposed that foot ulcers precede 84% of diabetes-related amputations and are a common diabetes-related cause of hospitalization [44, 45]. Moreover, patients with neuropathic diabetic foot ulceration have a 7% risk of amputation in the next 10 years [46].

Amputations

One of the more devastating outcomes of diabetic complications is the amputated limb. By definition, it is the failure of limb preservation methods and represents the most severe consequence of diabetes on the lower extremity. The leading cause of nontraumatic LEAs is diabetes [10], and greater than 80,000 procedures are performed annually. Some estimates have stated that the likelihood of amputation is 10–30 times higher among patients with diabetes than in the general population of the USA [47–52]. According to the Agency for Healthcare Research and Quality (AHRQ) National Quality Health Report, in the year 2007, the age-adjusted incidence of amputations attributable to diabetes was 33.6 per 100,000 among Americans of the age 18 and older [53] (Fig. 2.5). The US Department of Health and Human Services' Healthy People 2010 report states an objective of reducing diabetic amputations from the 1998 baseline of 6.6 per 1,000 to a target of 2.9 per 1,000 patients with diabetes. The Healthy People 2010 Midcourse review reported that at the time of the review 49% of the target reduction had been achieved, which translated to an incidence of 4.7 per 1,000 patients [54]. Several changes in the quality of care have occurred in the past decade including the adoption of the team approach [55–57] that may have led to these improvements. These are detailed extensively in another chapter. The incidence of amputations has persistently trended down despite an increase in the prevalence in diabetes overall [54, 58]. Despite these improvements, differences

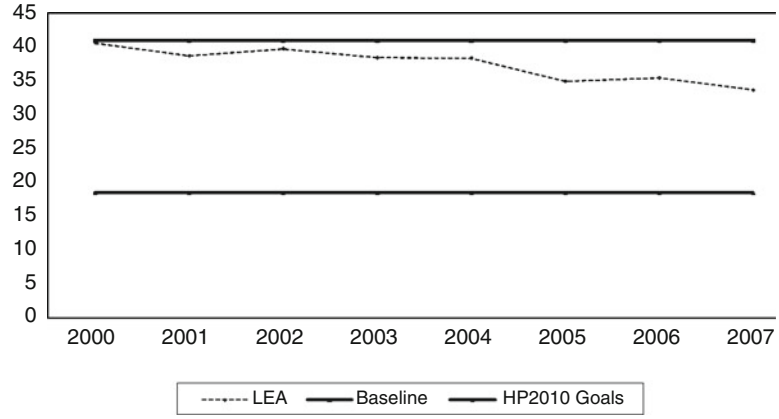

Fig. 2.5 Diabetes-associated lower extremity amputations per 100,000 population [53]

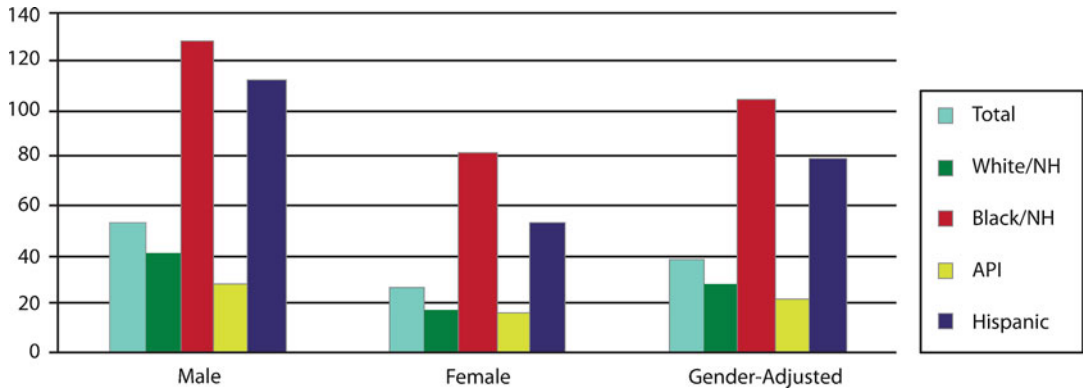

Fig. 2.6 Race-specific age-adjusted rates of amputation by gender per 100,000 general [61]

persist along demographic lines, including age, race, and gender. The causes of these inequalities are beyond the scope of this chapter but are included to facilitate a more complete epidemiologic understanding by the readers.

Gender Disparities

Numerous studies have provided support that men have a higher risk of amputation than women even after controlling for factors, such as age. This difference has been observed in amputations related to trauma as well as diabetes. Among individuals with diabetes, the risk of amputation appears to be two times greater in men [59]. As of 1999, the age-adjusted incidence was 4.1 per 1,000 for females and 9.2 per 1,000 in males. Six years later, in 2005, the age-adjusted rates were 2.6 per 1,000 and 5.6 per 1,000, respectively [60]. Although the overall incidence has decreased for both genders—37% reduction for women and 39% for men—the gap between the groups persists [60]. The disparity between men and women persists even along racial and ethnic lines (Fig. 2.6). Using data from 2004, White non-Hispanic males have a rate 2.4 times higher than females. In terms of gender disparity, this is followed by Hispanics at 2.1 and Asians/Pacific Islanders at 1.7, while Black/NH men have only a 1.56 higher incidence of amputations relative to Black/NH women [61].

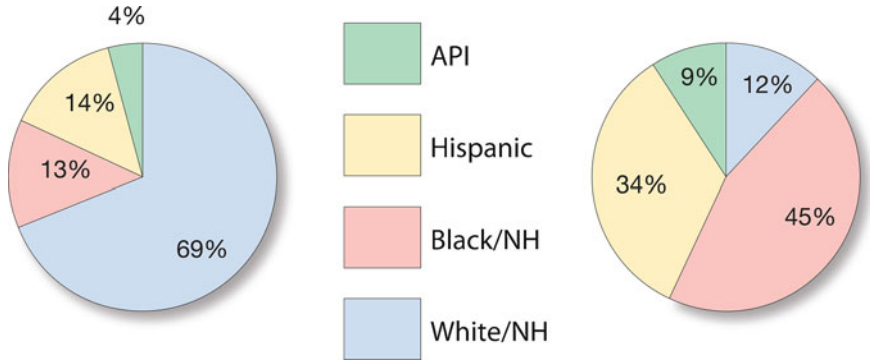

Fig. 2.7 *Left*: The US population projections by race and ethnicity [62]. *Right*: Proportion of diabetic LEA risk by race and ethnic divisions [61]

Racial and Ethnic Disparities

Differences in the incidence of diabetic amputation vary substantially among racial and ethnic groups, although the overall incidence rate has decreased over time. The racial and ethnic divisions that follow are broadly defined in the manner most frequently employed by the CDC, AHRQ, and other monitoring agencies. Because these sources are updated on an annual basis, they provide readers with a consistent reference for these figures. Incidence is discussed in terms of the rate per 1,000 persons with diabetes and the rate per 100,000 total population. Although the former calculation is the more informative from an epidemiologic perspective, it is also less accurate because of estimates made about the prevalence of diabetes. In most population-level studies, white non-Hispanic individuals frequently serve as the reference group in the USA. With this common reference, the risk of a White/NH diabetic patient would be equal to 1.0.

Despite having the smallest disparity between genders, Black/NH diabetic patients have the highest incidence of LEAs in the studied population. The incidence was 5.7 per 1,000 between 2004 and 2006, a rate 2.3 times higher than the 2.5 per 1,000 among White/NH during the same time period. If the general population is used as the denominator, then the risk is 3.8 times greater than White/NH Americans. The incidence rate attributed to Hispanics and Latinos was twice that found in White/NH per 1,000 diabetic patients, making them the second highest at-risk racial group. This ethnic group also has the largest gap between genders among minority populations. Finally, Asians and Pacific Islanders have a relative risk that is 23% lower than White/NH diabetics and also boast the second smallest disparity between males and females. As a group, Asian and Pacific Islanders had achieved 87% of the Healthy People 2010 goal by 2004. The US census estimates by racial and ethnic proportions in 2004 [62] and the proportion of risk among these categories [61] are shown in Fig. 2.7.

Socioeconomic Differences

Gender and racial/ethnic differences have been presented above, but beyond the scope of clinical characteristics are regional and socioeconomic determinants, which have also been reported as a source of disparate outcomes [63]. Socioeconomic status is a term that attempts to capture an individual's capacity to function within society. This is often measured using their level of education, annual income, or community of residence. Several studies support the proposal that lower socioeconomic status carries a higher likelihood of amputation [59, 64]. This impacts the overall health of an individual in many ways. Lower education can reduce an individual's health literacy, the understanding of one's health, and behaviors that promote a healthy lifestyle. It may also impair early recognition of pathology before it becomes limb threatening. Annual income may impact the means to seek or obtain care or purchase

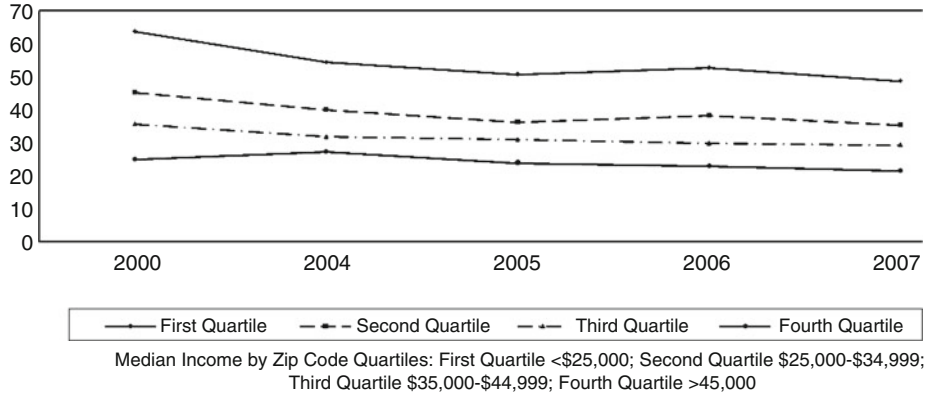

Fig. 2.8 LEA incidence by zip code median income [65]

supplies/medications to carry out treatments prescribed by the medical team. Lower income may also reflect an occupation that does not permit the absence from work in order to seek care.

The wealth of a community also can contribute to limitations in access to care and resources that can be directed to remove obstacles. An individual with an ulceration living in a wealthy community, where a specialized wound center was present and easily accessible to provide treatment, would be more likely to obtain care than an individual living in a resource-poor community, where the treatment options may be more limited and less effective in reducing the likelihood of progression. A frequently used proxy for community resources is the median income of a given zip code. Again, comparing data from 2004, the incidence of amputations was 33% higher in communities where the median income was less than $25,000 as compared to the incidence where the median income was $25,000–$34,999. This difference becomes even more substantial when compared to communities with a median income of $45,000 or more, where the incidence is 2.4 times greater in the under-$25,000 categories. Since the median income for the USA was $44,389 in 2004, these data suggests that the age- and gender-adjusted relative risk of amputation is between 25 and 240% higher for communities where the median income is below the national median than for communities where the median income is above the national median.

Between 2000 and 2007, the first quartile, representing the lowest median income, has realized a 23.4% reduction in incident diabetes LEAs ($p=0.0003$) (Fig. 2.8). Despite this positive outcome, as of 2007, the incidence in the highest quartile was 55% lower than that in the first quartile ($p<0.0001$) [65].

Outcomes

Amputations can vary based on the level and location of procedure along with the corresponding post-amputation complications. Each level carries with it different consequences ranging from shoe modifications to death. The two most pressing consequences are those of subsequent amputation and death. One study found that the overall reamputation rates were 26.7, 48.3, and 60.7% after 1, 3, and 5 years following the index amputation, respectively. In general, the more proximal the amputation, the higher the likelihood of a more severe complication [66]. During the first 12 months following a toe amputation, the risk of another amputation is 22.8% on the ipsilateral side and 3.5% on the contralateral side. Over a 5-year period, the risk increases to 52.3 and 29.5%, respectively. For midfoot amputations, 18.8% of patients required another amputation on the same side during the first year, and 9.4% required an amputation on the opposing limb during that same time. After 5 years, the incidence of amputation increases to 42.9% on the same limb and 33.3% on the contralateral limb. Individuals with either a transtibial or more proximal amputation had a reamputation proportion of

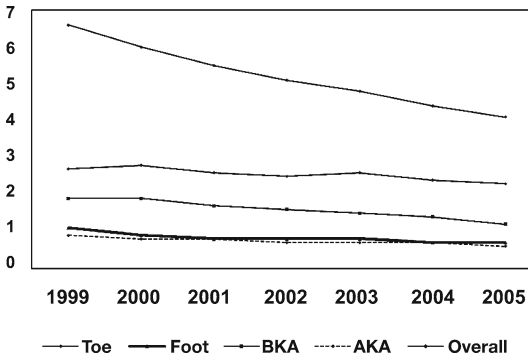

Fig. 2.9 Amputation rate per 1,000 patients with diabetes [12]

4.7 and 13.3% of the same extremity after 1 and 5 years, respectively. Surprisingly, a subsequent amputation of the contralateral limb occurred in 11.6% after 1 year and 53.3% after 5 years. It would be expected that a higher occurrence of additional amputations would be seen after distal procedures given the presence of more at-risk structures. These findings support an approach using frequent surveillance, careful monitoring, and post-amputation education to reduce the risk of subsequent amputations [49, 67].

An important distinction to make is the level of the amputation performed. The clinical relevance is detailed in the next section. Studies often distinguish between minor amputations (ICD-9 84.11 (toe), 84.12–84.13 (transmetatarsal), 84.14) and major amputations (84.15–84.16 (transtibial), 84.17–84.19 (transfemoral)) [49, 68]. Although this is not universally the protocol, it is frequently encountered. Figure 2.9 demonstrates that toe amputations are the most frequent, followed by below-the-knee amputations (BKAs). The trends show that a decline in the incidence is evident at all levels of amputation per 1,000 patients with diabetes [66, 68].

Mortality

A direct causal relationship between amputation and short-term mortality has not been proven, but a strong association between these variables has been shown in several studies [41, 69, 70]. One proposed mechanism is that the post-amputation exertion of gait stresses the cardiovascular system and increases the risk of a fatal cardiac event.

Amputation is not a benign outcome for either diabetic or nondiabetic patients. One study noted that the 1-, 5-, and 10-year mortality rates for nondiabetic individuals were 27.3, 57.2, and 77.1%, respectively. The study also noted that diabetic mortality was reported to be 32.8% after 1 year, 68.1% after 5 years, and 91.6% after 10 years. In the observed populations, the gap between the respective groups increased mortality rate from 5.5 to 14.5%. The authors concluded that diabetic patients had a 55% greater risk of death following amputation than nondiabetics, and that median survival was 27.2 and 46.7 months, respectively [49].

As noted with the risk of reamputation, the risk of mortality is also influenced by the level of the index amputation. Within 1 year of the index amputation, mortality rates for diabetic patients were 6.6% after digital amputations, 4.4% after ray amputations, 10.5% after midfoot amputations, and 18.2% after a major amputation. Extending this to 5 years from the initial amputation, toe and ray amputations had mortality rates of 26.2 and 15.8%, respectively. Five-year mortality after a major amputation was found to be 36%, while midfoot amputations carried a risk of 21% [66].

Perioperative Mortality

Perioperative mortality has been reported to be quite high following amputation. Mortality rates have ranged between 5.8 and 23% during the first 30 days following amputation [59, 71–75]. Patients requiring a guillotine amputation secondary to sepsis have a particularly high perioperative mortality rate of 14.3% (26). The most frequently cited 30-day mortality causes have been cardiac events and sepsis [59]. Short-term mortality following amputation is primarily related to cardiac events, with rates ranging from 28.5 to 52.2% [66, 71]. Sepsis is the second most frequent cause of death, with rates ranging from 14.2 to 26.1% [66, 71, 76]. The level of amputation again has an influence on this outcome. Two

distinct studies demonstrate similar 30-day mortality rates following above-the-knee (AKA) or below-the-knee amputations. Subramaniam et al. reported 17.5 and 4.2% mortality, while Stone et al. reported 17.6 and 3.6%, respectively [75]. The results by Stone et al. were more comprehensive and demonstrated a trend of increasing perioperative mortality as amputations became more proximal starting at the metatarsals and ending at the hip [77].

Cost of Lower Extremity Disease in Diabetes

Cost to the Health Care System

Thus far, this chapter has covered the epidemiologic aspects of the at-risk foot. The remaining portion focuses on the costs attributable to these conditions. Boulton et al. commented on the substantial economic burden that the diabetic foot places on the afflicted patient and the health care system, although they recognized that most estimates fail to account for preventive care, lost productivity, and rehabilitation. They further proposed that if these aspects were also added to the current estimates as much as 20% of diabetes costs could be associated with diabetic foot ulcers [78]. The excess costs are primarily attributable to more frequent hospitalization, use of antibiotics, and need for amputations and other surgical procedures [79].

Harrington and colleagues examined excess costs attributable to patients with diabetic foot ulcers vs. those with diabetes alone. Among the Medicare population sampled, they found that the direct costs per patient per year were $15,300 among patients with ulcers vs. $5,200 for patients without an ulcer [80].

Similar findings were noted in a health maintenance organization (HMO) population, where diabetic patients without ulcers had a cost per patient per year of $5,080 while it remained substantially higher for patients with an ulcer at $26,490 per patient per year [33, 81]. Costs also vary considerably based on ulcer grade. In a large insurance claims database, Stockl et al. observed that the cost of an ulcer episode ranged from $1,892 for a level 1 ulcer to $27,721 for level 4/5 ulcers [82]. Overall, inpatient hospital charges comprised 77% of total costs.

Table 2.2 Costs of various diabetic foot complications adjusted to the US currency in 1998 and 2010

	1998 ($)	2010 ($)
Diabetes without ulcer	5,402.17 [1] 5,433.33 [2]	7,225.35 [1] 7,267.03 [2]
Diabetes with ulcer	15,894.84 [1] 28,332.48 [2]	21,259.20 [1] 37,894.43 [2]
DM ulcer with primary healing	8,659 [3, 4]	11,581.33 [3, 4]
DM ulcer with amputation	43,270.44 [3, 4] 2,452 [5]	57,873.82 [3, 4] 3,279.53 [5]
DM major amputation	66,215 [3, 4] 45,343 [6]	88,561.95 [3, 4] 60,645.85 [6]
DM minor amputation	43,800 [3, 4] 19,996 [6]	58,582.10 [3, 4] 26,744.47 [6]

Costs can also be examined in the context of clinical outcomes, and significant differences exist among patients who achieve primary healing vs. amputation. Apelqvist et al. [69, 83, 84] found that the cost of primary healing was $6,800 per admission while Holzer et al. [85] found a smaller cost of $1,920 per episode; however, the cost jumped substantially if complicated by osteomyelitis ($3,580). In the same study, patients requiring an amputation had an associated cost of $15,790 per admission. Further cost comparisons can be made between patients who required amputation and those who did not need an amputation. The Apelqvist study reported that the average cost of amputation per admission was $45,870. Differences in cost via amputation level are also present, where the major amputations have been 1.5–2.3 times higher than minor amputations [69, 83, 84, 86]. Many of these study costs were drawn from different time periods, so for ease of interpretation Table 2.2 demonstrates currency values to 1998 and 2010 equivalents [87].

According to data from the national inpatient sample population, more proximal amputations have been associated with higher costs and longer lengths of stay (Table 2.3). This is likely attributable to the increased morbidity and mortality associated with major amputations. In 2008, the average length of stay was 47% longer

Table 2.3 Charges to hospitals for patients with diabetes by amputation level, 2008 [65]

		Diabetes with complications		Overall	
ICD-9	Amputation	Length of stay	Average charge ($)	Length of stay	Average charge ($)
84.11	Toe amputation	8.3	45,509	8.4	45,468
84.12	Amputation through foot	11.8	69,064	12.3	73,160
84.15	Below-the-knee amputation	12.2	68,542	12.8	77,577
84.17	Above-the-knee amputation	12.6	69,380	13.1	79,982

Table 2.4 Ulcer and amputation charges by hospitals for patients with diabetes, 2005 [65, 88]

		Medicare		Medicaid		Private	
		Length of stay	Average charge ($)	Length of stay	Average charge ($)	Length of stay	Average charge ($)
DRG	*Condition*						
271	Skin ulcers in diabetes with complications	9.8	26,937*	6.4	19,787	6.8	19,885
	Skin ulcers in diabetes without complications	9.8	25,803	7.8	25,429	8.2	25,395
199	Chronic ulcer in diabetes with complications	12.4	39,343	10.0	35,126	9.4	33,317
	Chronic ulcer in diabetes without complications	11.4	32,999	10.1	30,530	8.2	27,886
157	Lower extremity amputation in diabetes with complications	10.8	47,110	11.7	47,493	9.4	42,586

*Charges do not include professional fee

after a major amputation as compared to the mean stay after a toe amputation. Similarly, the mean charges were 53% higher after a major amputation relative to average toe amputations [88]. A comparison of length of stay and charges associated with ulcerations and amputations by insurance payer can be seen in Table 2.4 [65].

Cost-Effectiveness of Prevention

Most physicians and patients agree that prevention of lower extremity ulceration, infection, and amputation is the most desirable clinical strategy, and several studies have shown that this approach is either highly cost-effective or cost saving. In the UK, a 2-year prospective cohort study of 2,000 patients comparing a diabetic foot protection and screening program with conventional diabetes care demonstrated that only 24 patients in the protection program developed ulcers vs. 35 patients receiving conventional care. More importantly, only 7 of the patients with ulcers in the specialized program progressed to amputation, whereas 23 progressed in the conventional care group ($p<0.01$). The total cost of the screening program was only £100 per patient per year while producing a savings of 11 amputations in 1,000 patients at a cost of £12,084/amputation [89]. A retrospective cohort study from Austria using a Markov model to estimate long-term costs and outcomes in a dedicated screening program compared with conventional care similarly concluded that the screening program would reduce costs by 29.8% for mild (grade A) ulcers and by 49.7% for severe (grade D) ulcers, primarily due to lower amputation rates [90]. In a systematic review from the CDC on the cost-effectiveness of interventions to prevent diabetes and its complications, the use of comprehensive foot care to prevent ulcers was one of the few interventions found to be cost saving [91].

Evaluation of changes in quality of life, as reflected in cost–utility analysis, has shown similar results. Ortegon et al. used a Markov model to estimate lifetime risk of developing foot disease

among newly diagnosed patients with type 2 diabetes receiving optimal foot care guidelines, intensive glycemic control, or standard care [92]. In all simulations using a wide range of assumptions in the sensitivity analysis, use of guidelines for foot care resulted in longer life expectancy, improved quality of life, lower incidence of foot ulcers, and fewer LEAs when compared with standard care. Most simulations demonstrated that the costs were less than $25,000 per QALY gained compared to standard care. The best results were obtained when foot care guidelines were combined with intensive glycemic control, with a cost of $7,860 per QALY gained [92].

Summary

The diabetic limb is vulnerable to a variety of risk factors which have the potential to culminate in the onset of ulceration. Among patients with diabetes, the lifetime incidence of developing an ulcer is 15–25%. Wound healing may be a protracted process, and recurrent wounds are common during the first 2 months after closure [38].

Amputation is a devastating consequence of diabetic complications. Because of the intrinsic morbidity and mortality associated with amputations, diverse organizations have worked toward implementing plans to reduce amputation rates. In the USA, one such program includes the Healthy People 2010 objective to reduce the annual incidence of diabetic LEAs by 55%. By 2005, participating researchers had projected that a 29% reduction had been achieved despite an increase in diabetes prevalence by 35% during that same period [54]. The incidence for amputations consistently appears to be approximately twice as high for males as females [61]. Along racial and ethnic divisions, gender- and age-adjusted figures identify black non-Hispanics as the highest risk group and Asian/Pacific Islanders as the lowest [61]. Another high-risk group includes diabetic patients living in poor areas, where the median income is less than $25,000 annually. Although a large gap between the wealthiest and poorest quartiles persists, the largest magnitude of reduction has occurred in the poorest group [61].

The consequences of LEA can be severe, particularly in diabetic patients, where their 10-year mortality rate is nearly 20% higher than that in similar nondiabetic populations [49]. Even perioperative mortality is high, with rates between 5 and 23% reported in the first 30 days [59, 71–75]. This proportion can change depending on the level of the amputation performed. Digital and other "minor" amputations have a substantially lower mortality rate associated as compared to major amputations which may have a 5-year mortality rate of 36–69%. Subsequent amputations are also problematic, and as many as 68% of amputees will require further amputation within 5 years. This may be influenced by the level of the initial amputation, where digital amputations have a greater risk of reamputation than major amputations [67].

Health care costs associated with diabetic ulcers and amputations contribute significantly to the financial burden of diabetes. According to the US national inpatient sample, as of 2008, the total number of discharges attributed to diabetes-related amputations was projected to be 45,000. The average length of stay was 10.1 days with an in-hospital mortality proportion of 1.29%. The most frequent discharge statuses were to a rehabilitation facility (37.9%), routine discharge (31.5%), or home health care (26.9%). The mean charges were $56,216 while the aggregate charges for the year 2008 had a total of $2,548,319,965. However, it is worth noting that charges and actual cost frequently are separated by a wide margin. Length of stay in the hospital was 47% longer after a major amputation than a toe amputation. During that same time, charges following a major amputation were 53% higher than those after a digital amputation [65]. Importantly, measures aimed at preventing LED, including simple interventions such as following recommended guidelines, have been shown to be highly cost-effective in preventing ulcers and subsequent amputations.

Zimmet may have been correct to call diabetes a worldwide epidemic, as prevalence has climbed higher over the years [1, 3]. Even though the "at-risk" population has increased, the rates of limb-threatening complications have trended downward. The progressive deployment of the

"team approach" to limb preservation has been touted as a contributing factor, but patient education and vigilance should not be discounted for this success.

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Diabetic Polyneuropathy

3

Solomon Tesfaye

Abstract

Diabetic neuropathy is a common complication of diabetes and a cause of considerable morbidity and increased mortality. Diabetic neuropathy is not a single entity but encompasses several neuropathic syndrome. However, by far, the commonest presentation of neuropathy in diabetes is chronic distal symmetrical polyneuropathy also commonly known as diabetic peripheral neuropathy (DPN). The Toronto Diabetic Neuropathy Consensus Panel defined DPN as "a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure and cardiovascular risk covariates. An abnormality of nerve conduction (NC) tests, which is frequently subclinical, appears to be the first objective quantitative indication of the condition. The occurrences of diabetic retinopathy and nephropathy in a given patient strengthen the case that the polyneuropathy is attributable to diabetes". This chapter covers all the neuropathic syndromes encountered in diabetes mellitus, although the main focuses are (1) DPN, which is the main initiating factor for foot ulceration and a cause of troublesome chronic painful neuropathic symptoms, and (2) autonomic neuropathy, often associated with DPN that can involve almost all the systems of the body and may have devastating consequences, such as sudden death.

Keywords

Epidemiology • Symmetrical polyneuropathies • Diabetic peripheral neuropathy • Small-fibre neuropathy • Focal neuropathies • Multifocal neuropathies • Proximal motor neuropathy • Cranial mono-neuropathies • Thoraco abdominal neuropathy • Pressure palsies • Carpal tunnel syndrome • Pathogenesis of DPN • Vascular factors • Autonomic neuropathy • Diabetic peripheral neuropathy • Tricyclic antidepressants

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Introduction

Diabetic neuropathy is a common complication of diabetes and a cause of considerable morbidity and increased mortality [1]. Diabetic neuropathy is not a single entity but encompasses several neuropathic syndromes (Fig. 3.1). However, by far, the commonest presentation of neuropathy in diabetes is chronic distal symmetrical polyneuropathy also commonly known as diabetic peripheral neuropathy (DPN). The Toronto Diabetic Neuropathy Consensus Panel defined DPN as "a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure and cardiovascular risk covariates. An abnormality of nerve conduction (NC) tests, which is frequently subclinical, appears to be the first objective quantitative indication of the condition. The occurrences of diabetic retinopathy and nephropathy in a given patient strengthen the case that the polyneuropathy is attributable to diabetes" [1]. This chapter covers all the neuropathic syndromes encountered in diabetes mellitus depicted in Fig. 3.1, although the main focuses are (1) DPN, which is the main initiating factor for foot ulceration and a cause of troublesome chronic painful neuropathic symptoms, and (2) autonomic neuropathy, often associated with DPN that can involve almost all the systems of the body and may have devastating consequences, such as sudden death.

Epidemiology

The prevalence of DPN varies according to what tests are employed to detect neuropathy. When electrophysiology is employed to assess disease presence, the prevalence rates will be in excess of 50% [2], whereas when clinical parameters and/or quantitative sensory testing (QST) are employed both clinic- and population-based studies show surprisingly similar prevalence rates for DPN, affecting about 30% of all diabetic people [3]. The EURODIAB Prospective Complications Study investigated 3,250 type 1 patients, from 16 European countries, and found a prevalence rate of 28% for DPN at baseline [4]. The study also showed that over a 7.3-year period about one-quarter of type 1 diabetic patients developed DPN, age, duration of diabetes and poor glycaemic control being major determinants [5]. The development of DPN was also associated with potentially modifiable cardiovascular risk factors, such as hypertension, hyperlipidaemia

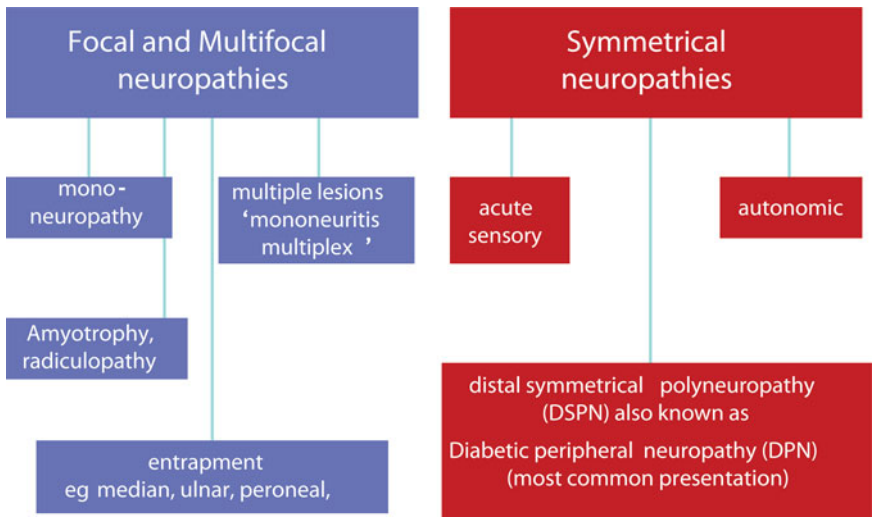

Fig. 3.1 Neuropathic syndromes associated with diabetes mellitus

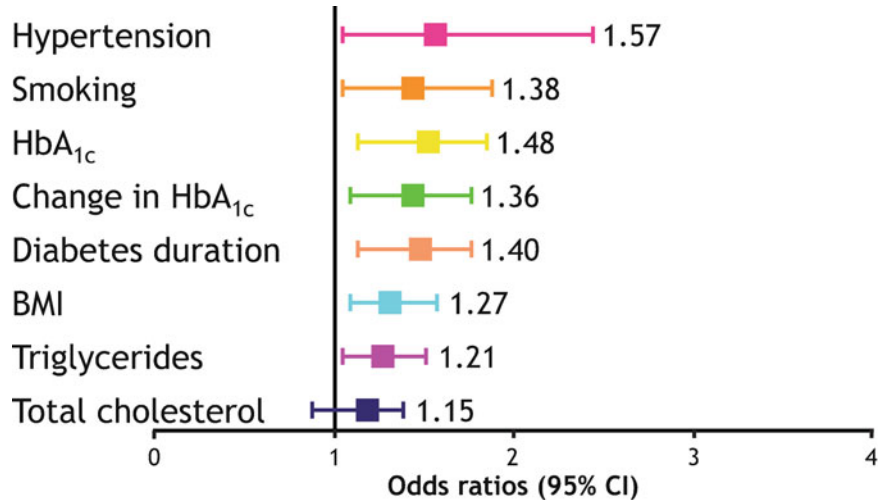

Fig. 3.2 Risk factors for incident DPN in the EURODIAB prospective study showing odds ratios for the various risk factors for DPN in a cohort of 1101 type 1 diabetes mellitus patients followed for 7.3 ± 0.6 years. BMI, body mass index; CVD, cardiovascular disease

(in particular hypertryglyceridaemia), obesity and cigarette smoking (Fig. 3.2) [5]. Based on recent epidemiological studies, correlates of DPN include increasing age, increasing duration of diabetes, poor glycaemic control, retinopathy, albuminuria and vascular risk factors [5].

Symmetrical Polyneuropathies

Diabetic Peripheral Neuropathy

Clinical Presentation: History

The onset of DPN is heralded by a "length-related" pattern of sensory loss, i.e. sensory symptoms that start in the toes and then progress proximally to involve the feet and legs in a stocking distribution. When the disease is well established in the lower limbs in more severe cases, there is often upper limb involvement, with a similar progression proximally starting in the fingers. Although the nerve damage can extend over the entire body including the head and face, this is extremely rare. Autonomic neuropathy usually accompanies DPN, and subclinical autonomic neuropathy detectable by autonomic function tests is usually present. However, obvert clinical autonomic neuropathy is less common. As the disease advances, overt motor manifestations, such as wasting of the small muscles of the hands and limb weakness, become apparent. However, subclinical motor involvement detected by magnetic resonance imaging appears to be common, and thus motor disturbance is clearly part of the functional impairment caused by DPN [6].

The main clinical presentation of DPN is sensory loss, which the patient may not be aware of, or may be described as "asleep numbness" or "dead feeling". However, some may experience a progressive build-up of unpleasant sensory symptoms, including tingling (paraesthesiae or "pins and needles"); burning pain; shooting pains down the legs ("like electric shock"); lancinating pains ("knife like"); contact pain often with daytime clothes and bedclothes (allodynia); pain on walking often described as "walking barefoot on marbles" or "walking barefoot on hot sand or broken glass"; sensations of heat or cold in the feet and persistent achy feeling in the feet and cramp-like sensations in the legs. Occasionally, pain can extend above the feet and may involve the whole of the legs, and when this is the case, there is usually upper limb involvement also. Figure 3.3 shows the "positive" and "negative"

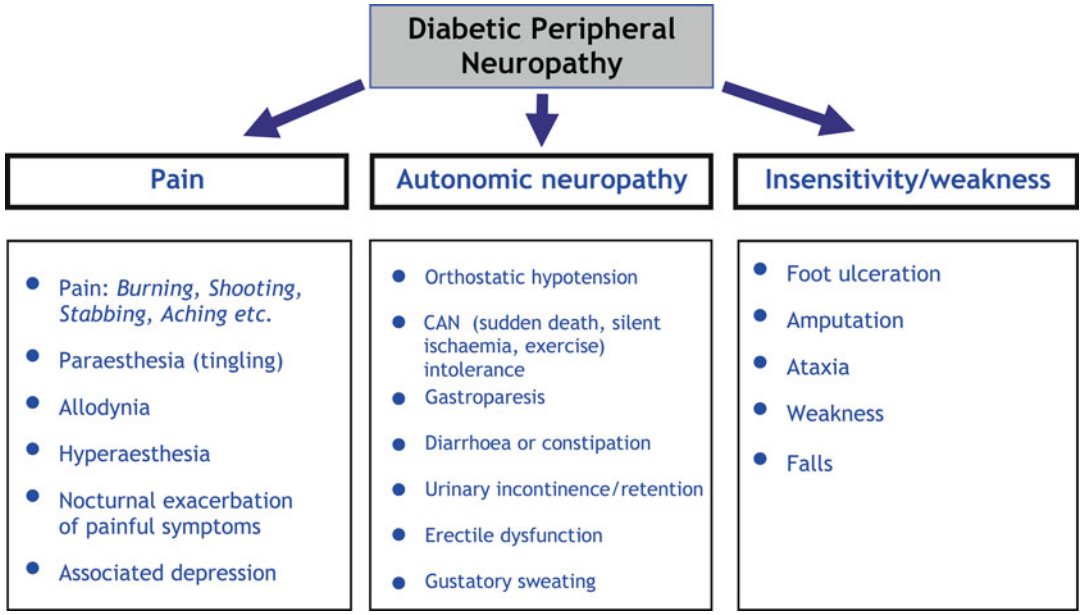

Fig. 3.3 Symptoms of DPN

symptoms of DPN. There is a large spectrum of severity of these symptoms. Some may have minor complaints, such as tingling in one or two toes; others may be affected with the devastating complications, such as "the numb diabetic foot" or severe painful neuropathy that does not respond to drug therapy.

Diabetic neuropathic pain is characteristically more severe at night, and often prevents sleep [7, 8]. Some patients may be in a constant state of tiredness because of sleep deprivation [7]. Others are unable to maintain full employment [9]. Severe painful neuropathy can occasionally affect one's ability to walk and hence may have a negative impact on day to day functionality [9]. This is particularly the case when there is an associated disabling, severe postural hypotension due to autonomic involvement. Not surprisingly therefore, depressive symptoms are not uncommon [9]. Although, subclinical autonomic neuropathy is commonly found in patients with DPN [10], symptomatic autonomic neuropathy is uncommon. It is also important to appreciate that many subjects with DPN may not have any of the above symptoms, and their first presentation may be with a foot ulcer [11]. Thus, there is a sound reason for the need to carefully examine and screen the feet of all diabetic people in order to identify those at risk of developing foot ulceration. The insensate foot is at risk of developing mechanical and thermal injuries, and patients must therefore be warned about these and given appropriate advice with regard to foot care [11]. A curious feature of the neuropathic foot is that both numbness and pain may occur, the so-called "painful, painless" leg first described by John Ward [12]. It is indeed a paradox that the patient with a large foot ulcer may also have severe neuropathic pain. In those with advanced neuropathy, there may be sensory ataxia. The unfortunate sufferer is affected by unsteadiness on walking, and even falls particularly if there is associated visual impairment due to retinopathy. Figure 3.4 shows the clinical consequences of DPN. Autonomic presentations are discussed below.

Clinical Diagnosis: Examination

DPN is usually easily detected by simple clinical examination (Table 3.1) [13]. Shoes and socks should be removed and the feet examined at least

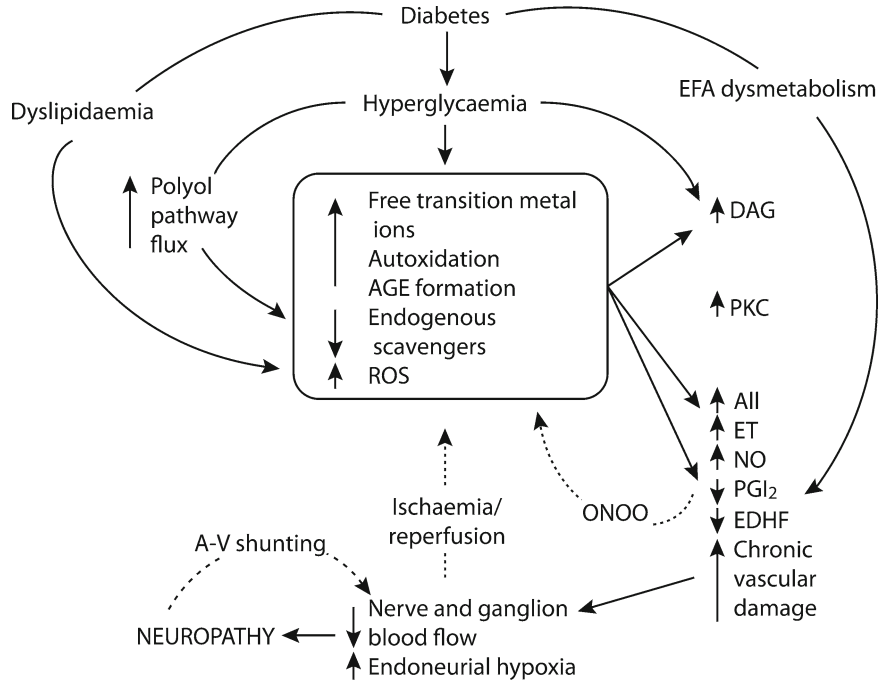

Fig. 3.4 Clinical consequences of diabetic peripheral neuropathy

Table 3.1 Clinical assessment for DPN

History	Signs
Sensory symptoms	Inspection (normal or distal wasting, clawing)
Motor symptoms	Reflexes (ankle reflex unreliable in the elderly)
Assessment of disability	Sensory
Exclude other causes of neuropathy	Vibration Light touch Pinprick (good discriminator in the elderly) 10 g Mono-filament Assess footwear

In DPN there is a reduction in reflexes, vibration, pinprick and pressure sensation

annually and more often if neuropathy is present. The most common presenting abnormality is a reduction or absence of vibration sense in the toes. As the disease progresses, there is sensory loss in a "stocking" and sometimes in a "glove" distribution involving all modalities. When there is severe sensory loss, proprioception may also be impaired, leading to a positive Romberg's sign. Ankle tendon reflexes are lost (though this may also be lost with old age in non-diabetic people) and with more advanced neuropathy, knee reflexes are often reduced or absent.

Muscle strength is usually normal early during the course of the disease, although mild weakness may be found in toe extensors. However, with progressive disease, there is significant generalised muscular wasting, particularly in the small muscles of the hand and feet. The fine movements of fingers would then be affected, and there is difficulty in handling small objects. Wasting of dorsal interossei is, however, usually due to entrapment of the ulnar nerve at the elbow. The clawing of the toes is believed to be due to unopposed (because of wasting of the small muscles of the foot) pulling of the long extensor and flexor tendons. This scenario results in elevated plantar pressure points at the metatarsal heads that are prone to callus formation and foot ulceration. Deformities, such as a bunion, can form the focus of ulceration and with more extreme deformities, such as those associated with Charcot arthropathy [14], the risk is further increased. As one of the most common precipitants to foot ulceration

Table 3.2 Staged severity of DPN

Grade 0	No abnormality of NC; e.g., Σ 5 NC nds <95th percentile or another suitable NC criterion
Grade 1a	Abnormality of NC; e.g., Σ 5 NC nds ≥95th percentile without symptoms or signs
Grade 1b	NC abnormality of stage 1a plus neurological signs typical of DPN but without neuropathy symptoms
Grade 2a	NC abnormality of stage 1a with or without signs (but if present less than 2b) and with typical neuropathic symptoms
Grade 2b	NC abnormality of stage 1a, a moderate degree of weakness (i.e. 50%) of ankle dorsiflexion with or without neuropathy symptoms

DPN, diabetic peripheral neuropathy; NC, nerve conduction; nds, normal deviates

is inappropriate footwear, a thorough assessment should also include examination of shoes for poor fit, abnormal wear and internal pressure areas or foreign bodies.

Autonomic neuropathy affecting the feet can cause a reduction in sweating and consequently dry skin that is likely to crack easily, predisposing the patient to the risk of infection. The "purely" neuropathic foot is also warm due to arterio-venous shunting first described by Ward [15]. This results in the distension of foot veins that fail to collapse even when the foot is elevated. It is not unusual to observe a gangrenous toe in a foot that has bounding arterial pulses, as there is impairment of the nutritive capillary circulation due to arterio-venous shunting. The oxygen tension of the blood in these veins is typically raised [16]. The increasing blood flow brought about by autonomic neuropathy can sometimes result in neuropathic oedema, which is resistant to treatment with diuretics but may occasionally respond to treatment with ephedrine [17].

Autonomic neuropathy affecting the feet can cause a reduction in sweating and consequently dry skin that is likely to crack easily, predisposing the patient to the risk of infection. The neuropathic foot without peripheral vascular disease is also warm due to arterio-venous shunting and distended veins as a result of autonomic neuropathy [15, 16].

Assessing Severity of DPN

For a given patient, it may not be adequate to make the diagnosis of the presence of neuropathy; assessing the severity of DPN may be necessary particularly in the context of research studies and clinical trials. Similar to other complications of diabetes such as retinopathy and nephropathy, it may be desirable to assess the severity of DPN. The Toronto Diabetic Neuropathy Consensus Panel suggested a reliable objective and quantitative measure, i.e. NC abnormality as the minimal criteria for the diagnosis of DPN [1]. When NC values have not been assessed, the Consensus Panel recommends that it is not possible to provide a "confirmed" diagnosis of DPN—only a "possible" or "probable" diagnosis. There are several instruments that evaluate combinations of neuropathy symptoms, signs and neurophysiological test abnormalities giving scores for severity of DPN [18–20]. For clinical trials where accurate assessment of DPN is necessary, the following approach to estimating severity suggested by Dyck et al. can be used (Table 3.2) [1, 21]. It is important to exclude other causes of sensorimotor polyneuropathy. For epidemiological surveys or controlled clinical trials of DPN, the Toronto Consensus Panel advocated the use of an NC test as an early and reliable indicator of the occurrence of this neuropathy [1]. The group also emphasized that to be reliable the test must be carried out rigorously using appropriate reference values corrected for applicable variables [1]. Recent studies emphasize the importance of the proficiency of the clinical neurological assessment [1, 22, 23].

Differential Diagnosis of DPN

Before attributing the neuropathy to diabetes, other common causes of neuropathy must be excluded. The absence of other complications of diabetes, rapid weight loss, excessive alcohol intake and other atypical features in either the history or clinical examination should direct the physician to search for other causes of neuropathy (Table 3.3).

Table 3.3 Differential diagnosis of DPN

Metabolic
Diabetes
Amyloidosis
Uraemia
Myxoedema
Porphyria
Vitamin deficiency (thiamine, B12, B6, pyridoxine)
Drugs and chemicals
Alcohol
Cytotoxic drugs, e.g. Vincristine
Chlorambucil
Nitrofurantoin
Isoniazid
Neoplastic disorders
Bronchial or gastric carcinoma
Lymphoma
Infective or inflammatory
Leprosy
Guillain–Barre syndrome
Lyme borreliosis
Chronic inflammatory demyelinating polyneuropathy (CIDP)
Polyarteritis nodosa
Genetic
Charcot–Marie–Tooth disease
Hereditary sensory neuropathies

Acute Painful Neuropathies

Acute painful neuropathies are transient neuropathic syndromes characterised by an acute onset of pain (weeks rather than months) in the lower limbs. They are relatively rare compared to chronic DPN. There is often severe neuropathic pain involving both limbs that is distressing to the patient. There are two distinct syndromes, the first of which occurs within the context of poor glycaemic control and the second with rapid improvement in glycaemic control.

Acute Painful Neuropathy of Poor Glycaemic Control

This syndrome occurs usually in type 1 or type 2 diabetic subjects with poor glycaemic control. There is often an associated severe weight loss [24]. Ellenberg was the first to describe this condition as "neuropathic cachexia" [25]. Patients typically experience persistent burning pain associated with allodynia (non-painful stimulus perceived as painful). The pain is most marked in the feet but often affects the whole of the lower extremities. As in chronic DPN, the pain is typically worse at night, although unremitting pain during daytime is also common. The acute-onset distressing pain often results in depression.

In acute painful neuropathies, sensory loss is usually surprisingly mild or even absent. There are usually no motor signs, although ankle jerks may be absent. Nerve conduction studies are also usually normal or mildly abnormal. Temperature discrimination threshold (small-fibre function) is, however, affected more commonly than vibration perception threshold (large-fibre function). Studies are required to investigate if there is loss of intra-epidermal nerve fibre density which may be considered the gold standard in detecting small-fibre neuropathy [26]. There is complete resolution of symptoms within 12 months, and weight gain is usual with continued improvement in glycaemic control with the use of insulin.

Acute Painful Neuropathy of Rapid Glycaemic Control (Insulin Neuritis)

The term "insulin neuritis" which is often used to describe this syndrome is a misnomer as the condition can follow rapid improvement in glycaemic control with oral hypoglycaemic agents. The author has, therefore, recommended that the term "acute painful neuropathy of rapid glycaemic control" be used to describe this condition [27]. The natural history of acute painful neuropathies is an almost guaranteed improvement [27] in contrast to chronic DPN. The patient presents with burning pain, paraesthesiae and allodynia, often with a nocturnal exacerbation of symptoms; and depression may be a feature. There is no associated weight loss, unlike acute painful neuropathy of poor glycaemic control. Sensory loss is often mild or absent, and there are no motor signs. There is little or no abnormality on nerve conduction studies. Prognosis is good with usually complete resolution of symptoms within 12 months. The management of painful symptoms is as in chronic DPN (see page x).

Small-Fibre Neuropathy

The existence "small-fibre neuropathy" as a distinct entity has been advocated by some authorities [26, 28, 29] usually within the context of young type 1 patients and pre-diabetes [30]. A dominant feature of this syndrome is neuropathic pain, which may be very severe, with relative sparing of large-fibre functions (e.g. vibration and proprioception). The pain is described as burning, deep and aching. The sensation of pins and needles (paraesthesiae) is also often experienced. Contact hypersensitivity may be present. However, rarely, patients with small-fibre neuropathy may not have neuropathic pain, and some may occasionally have foot ulceration. Autonomic involvement is common, and severely affected patients may be disabled by postural hypotension and/or gastrointestinal (GI) symptoms. The syndrome tends to develop within a few years of diabetes (and indeed in pre-diabetes) as a relatively early complication.

On clinical examination, there is little evidence of objective signs of nerve damage, apart from a reduction in pinprick and temperature sensation, which are reduced in a "stocking" and "glove" distribution. There is relative sparing of vibration and position sense (due to relative sparing of the large-diameter Aβ fibres). Muscle strength is usually normal and reflexes are also usually normal. However, autonomic function tests are frequently abnormal and affected male patients usually have erectile dysfunction. Electrophysiological tests are usually normal. QST to assess the psychophysical thresholds for cold and warm sensations and skin biopsy with quantification of somatic intra-epidermal nerve fibres (IENFs) have been used to determine the damage to small nerve fibres.

Controversy still exists as to whether small-fibre neuropathy is a distinct entity or an earlier manifestation of DPN [28, 29]. Said et al. [28] studied a small series of subjects with this syndrome and showed that small-fibre degeneration predominated morphometrically. Veves et al. [31] found a varying degree of early small-fibre involvement in DPN which was confirmed by detailed sensory and autonomic function tests. It is unclear, therefore, whether this syndrome is in fact distinct or merely represents the early stages of DPN that has been detected by the prominence of early symptoms. The emergence of skin IENF as a marker of small-fibre damage may help to clarify the situation [32, 33].

Focal and Multifocal Neuropathies

Focal/multifocal (or asymmetrical) neuropathies have a relatively rapid onset, and complete recovery is usual. This contrasts with chronic DPN, where there is usually no improvement in symptoms several years after the onset. Unlike DPN, their presence is not related to the presence of other diabetic complications. Asymmetrical neuropathies predominantly affect middle-aged/older patients and are more common in men [34]. A high index of suspicion for a non-diabetic cause by conducting careful history/examination in order to identify any associated symptoms/signs is advisable. The clinical impact of these focal syndromes can sometimes be devastating as there is a relatively rapid onset and there may be marked weakness of a limb/s bordering on paralysis.

Proximal Motor Neuropathy (Diabetic Amyotrophy, Femoral Neuropathy)

The condition of progressive asymmetrical proximal leg weakness and atrophy was first described by Garland [35], who coined the term "diabetic amyotrophy". This condition has also been named as "proximal motor neuropathy" or "femoral neuropathy". The patient presents with severe pain which is felt deep in the thigh, but can sometimes be of burning quality and extend below the knee. The pain is usually continuous and often causes insomnia and depression [36]. Both type 1 and type 2 patients over the age of 50 are affected [35–37]. There is an associated weight loss which can sometimes be very severe, and can raise the possibility of an occult malignancy.

On examination, there is usually an asymmetrical profound wasting of the quadriceps with

marked weakness in these muscle groups, although hip flexors and hip abductors can also be affected. Thigh adductors, glutei and hamstring muscles may also be involved. The knee jerk is usually reduced or absent. The profound weakness can lead to difficulty from getting out of a low chair or climbing stairs. Sensory loss is unusual, and if present indicates a coexistent DPN.

Other causes of quadriceps wasting, such as nerve root and cauda equina lesions, and occult malignancy causing proximal myopathy syndromes (e.g. polymyocytis) should be excluded. MR imaging of the lumbo-sacral spine is now mandatory in order to exclude focal nerve root entrapment and other pathologies. An erythrocyte sedimentation rate (ESR), an X-ray of the lumbar/sacral spine, a chest X-ray and ultrasound of the abdomen may also be required. Electrophysiological studies may demonstrate increased femoral nerve latency and active denervation of affected muscles. CSF protein is often elevated.

The cause of diabetic proximal motor neuropathy is not known. It tends to occur within the background of DPN [38]. Some have suggested that the combination of focal features superimposed on diffuse peripheral neuropathy may suggest vascular damage to the femoral nerve roots as a cause of this condition [39].

As in DPN, there is scarcity of prospective studies that have looked at the natural history of proximal motor neuropathy. Coppack and Watkins [36] have reported that pain usually starts to settle after about 3 months, and usually settles by 1 year, while the knee jerk is restored in 50% of the patients after 2 years. Recurrence on the other side is a rare event. Management is largely symptomatic and supportive. Patients should be encouraged and reassured that this condition is likely to resolve. There is still controversy as to whether the use of insulin therapy influences the natural history of this syndrome. Some patients benefit from physiotherapy that involves extension exercises aimed at strengthening the quadriceps. The management of pain in proximal motor neuropathy is similar to that of painful DPN (see below).

Cranial Mono-Neuropathies

The third cranial nerve palsy is the commonest cranial mono-neuropathy encountered in diabetes. The patient presents with pain in the orbit or sometimes with a frontal headache [40, 41]. There is typically ptosis and ophthalmoplegia, although the pupil is usually spared [42, 43]. Recovery occurs usually over 6 months. The clinical onset and timescale for recovery, and the focal nature of the lesions on the third cranial nerve, on post-mortem studies suggested an ischaemic etiology [40, 44]. It is important to exclude any other cause of third cranial nerve palsy (aneurysm or tumour) by CT or MR scanning, where the diagnosis is in doubt. Fourth, sixth and seventh cranial nerve palsies have also been described in diabetic subjects, but the association with diabetes is not as strong as that with third cranial nerve palsy.

Thoraco-Abdominal Neuropathy (Truncal Radiculopathy)

Thoraco-abdominal neuropathy (truncal radiculopathy) associated with diabetes is characterised by an acute onset pain in a dermatomal distribution over the thorax or the abdomen [45]. The pain is usually asymmetrical, and can cause local bulging of the muscle [46]. There may be patchy sensory loss, and other causes of nerve root compression should be excluded. Recovery is usually the rule within several months, although symptoms can sometimes persist for a few years. Some patients presenting with abdominal pain have undergone unnecessary investigations, such as barium enema, colonoscopy and even laparotomy, when the diagnosis could easily have been made by careful clinical history and examination.

Pressure Palsies

Carpal Tunnel Syndrome

The patient typically has pain and paraesthesia in the hands, which sometimes radiate to the forearm and are particularly marked at night.

In severe cases, clinical examination may reveal a reduction in sensation in the median territory in the hands and wasting of the muscle bulk in the thenar eminence. The clinical diagnosis is easily confirmed by median nerve conduction studies and treatment involves surgical decompression at the carpel tunnel in the wrist. There is generally good response to surgery, although painful symptoms may relapse more commonly than in the non-diabetic population.

Ulnar Nerve and Other Isolated Nerve Entrapments

Pressure damage at the elbow can result in ulnar nerve palsy resulting in wasting of the dorsal interossei, particularly the first dorsal interossius. This is easily confirmed by ulnar electrophysiological studies.

Rarely, the patients may present with wrist drop due to radial nerve palsy after prolonged sitting (with pressure over the radial nerve in the back of the arms) while unconscious during hypoglycaemia or asleep after an alcohol binge.

In the lower limbs, the common peroneal (lateral popliteal) is the most commonly affected nerve resulting in foot drop. Unfortunately, complete recovery is not usual. The lateral coetaneous nerve of the thigh is occasionally also affected with entrapment neuropathy in diabetes. Phrenic nerve involvement in association with diabetes has also been described.

Pathogenesis of DPN

The pathogenesis of DPN remains undetermined [47] despite considerable research over many decades. Morphometric studies have demonstrated that DPN is characterised by pathological changes, including (1) axonal loss distally, with a "dying back" phenomenon [28]; (2) a reduction in myelinated fibre density [48] and (3) focal areas of demyelination on teased fibre preparations [28]. Nerve regenerative activity may also be seen with the emergence of "regenerative clusters" [49], containing groups of myelinated axons and non-myelinated axon sprouts. However, the small and unmyelinated fibres that make up around 80% of all nerve fibres have proved more difficult to assess.

Figure 3.5 shows the current thinking regarding the pathogenesis of diabetic neuropathy [50]. Hyperglycaemia stimulates the production of advanced glycosylated end products, activates protein kinase C, enhances polyol pathway activity and induces a dysregulation of reactive oxygen and nitrogen-generating pathways (nitrosative stress) [51]. These processes impair the capacity of the vascular endothelium to produce biologically active nitric oxide (NO), which adversely affects vascular relaxations. Endotheilal cells exposed to high extracellular glucose respond by increased mitochondrial superoxide formation [52]. Superoxide combined with NO generated by the endothelial cells (produced by the endothelial isoform of NO synthase) then leads to the formation of peroxynitrite, which attacks various biomolecules in the vascular endothelium [53]. Reactive oxygen and nitrogen species trigger endothelial cell dysfunction through many mechanisms, including substrate depletion and uncoupling of endothelial isoform of NO synthase [53]. Another pathomechanism involves DNA strand breakage and activation of the nuclear enzyme poly(ADP-ribose) polymerase (PARP). PARP activation, an important factor in the pathogenesis of diabetes complications, is considered a downstream effector of oxidative-nitrosative stress [53]. However, there is evidence that PARP activation may even precede and contribute to free radical- and oxidant-induced injury [54]. PARP-mediated poly(ADP-ribosyl)ation and inhibition of glyceraldehyde-3-phosphate dehydrogenase importantly contribute to the development of diabetic vascular complications: they induce the activation of multiple pathways of injury, including activation of nuclear factor kappa B, activation of protein kinase C and generation of intracellular advanced glycation end products [53]. Reactive species generation and PARP play key roles in the pathogenesis of "glucose memory" and development of injury in endothelial cells exposed to alternating high/low-glucose concentrations.

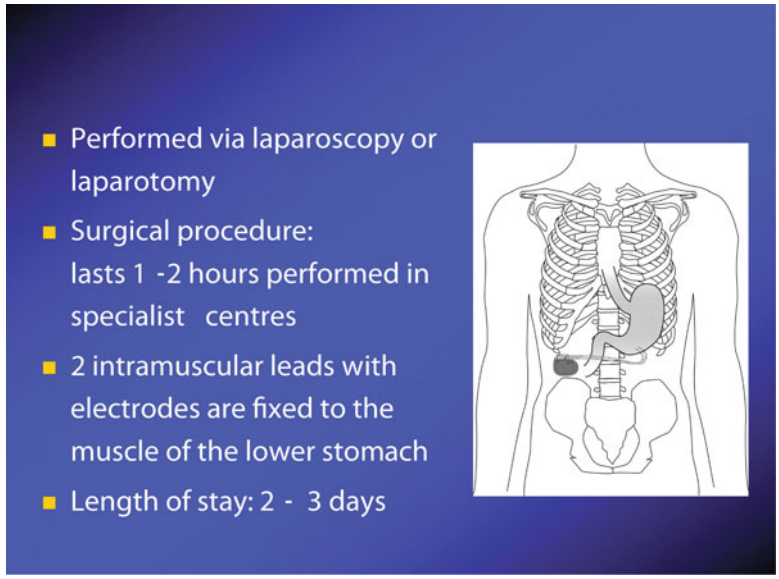

Fig. 3.5 Pathogenesis of DPN. Schematic of the metabolic and vascular interactions that alter neurovascular function in diabetes. *AII* angiotensin 2; *AGE* advanced glycation end product; *A-V* arterio-venous; *DAG* diacylglycerol; *EDHF* endothelium-derived hyperpolarising factor; *EFA* essential fatty acid; *ET* endothelin-1; *NO* nitric oxide; *ONOO-* peroxynitrite; *PGI2* prostacyclin; *PKC* protein kinase; *ROS* reactive oxygen species *(reprinted with kind permission of Springer Science + Busniess Media, LLC, Cameron NE, Eaton SE, Cotter MA, Tesfaye S. Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. Diabetologia 2001; 44: 1973–1988)*

Vascular Factors in the Pathogenesis of DPN

The view that micro-vessel disease may be central to the pathogenesis of diabetic neuropathy is not new. Severe neural microvascular disease has been demonstrated in subjects with clinical diabetic neuropathy [55]. Several workers have reported basal membrane thickening of endoneurial capillaries, degeneration of pericytes and hypoplasia and swelling of endothelial cells and sometimes vessel closure. The degree of microvascular disease has been correlated with the severity of neuropathy [56].

In vivo studies looking at the exposed sural nerve in human subjects have demonstrated epineural arterio-venous shunting, which appears to result in a "steal" phenomenon diverting blood from the nutritive endoneurial circulation [57]. The consequent impairment of nerve blood flow causes a fall in endoneural oxygen tension [58]. In addition, several other studies provide indirect evidence supporting a vascular aetiology for diabetic neuropathy. Strenuous exercise increases nerve blood flow, and thereby increases nerve conduction velocity by an average of 4 m/s in non-neuropathic diabetic subjects [59]. However, this significant increase in nerve conduction velocity, with exercise, is absent in neuropathic subjects as the nerve microvasculature is severely diseased [59]. Moreover, there is a strong correlation between nerve conduction velocity and lower limb transcutaneous oxygenation measurements in diabetes; macrovascular disease appears to exacerbate neuropathy and surgical restoration of perfusion improves nerve conduction velocity [60]. A recent epidemiological study has also found a strong correlation between diabetic neuropathy and cardiovascular risk factors, including body weight, hypertension, smoking and hypertriglyceridemia [5].

In addition to human studies, impairment of blood flow has been found to be an early feature

Table 3.4 Some of the clinical consequences of autonomic neuropathy

Cardiovascular autonomic neuropathy
Sudden death
Silent myocardial ischaemia
Exercise intolerance
Orthostatic hypotension
Resting tachycardia
Post-prandial hypotension
Left ventricular dysfunction
QT interval prolongation
Foot vein distension/arterio-venous shunting
Leg/foot oedema
Gastrointestinal autonomic neuropathy
Gastroparesis
Diarrhoea or constipation
Bladder hypomotility
Urinary incontinence/retention
Erectile dysfunction
Gustatory sweating
Impaired thermoregulation
Impaired papillary function

in rats with streptozotocin diabetes. Several vasodilators have also been found to enhance nerve blood flow and nerve function in diabetic animals [50]. In human diabetic neuropathy, ACE inhibitors have been found to improve nerve function [61, 62]. The presence of severe microvascular changes in subjects with acute painful neuropathy of rapid glycaemic control (insulin neuritis), hitherto thought to be purely metabolic in origin, provides an even more compelling evidence for the importance of microvascular factors in the pathogenesis of DPN [27].

Autonomic Neuropathy

Autonomic neuropathy can affect many systems (Table 3.4) and can be a cause of morbidity and sudden death. Although abnormalities of autonomic function detected by autonomic function tests are common in subjects with long-standing diabetes, clinically significant autonomic dysfunction is fortunately less uncommon. Autonomic neuropathy has a gradual onset and is slowly progressive. Subclinical autonomic neuropathy can often be identified by quantitative functional testing within 12 months of diagnosis in patients with type 2 diabetes and within a couple of years in those with type 1 diabetes [63]. The prevalence of diabetic autonomic neuropathy depends on the type of population studied and a number of tests of autonomic function employed. In the EURODIAB study, the prevalence of autonomic neuropathy defined as the presence of two abnormal cardiovascular autonomic function tests was 23.4 per 1,000 patient years, and the incidence increased with age, duration of diabetes, glycaemic control and presence of cardiovascular risk factors [64]. Intensive glycaemic control is critical in preventing the onset and slowing the progression of diabetic autonomic neuropathy. The Diabetes Complications and Control Trial (DCCT) showed that intensive glycaemic control reduced the prevalence of autonomic dysfunction by 53% [65].

Cardiovascular Autonomic Neuropathy

The Toronto Consensus panel has recently comprehensively reviewed cardiovascular autonomic neuropathy (CAN) and the reader is recommended to refer to the publications [66]. CAN is a serious complication of long-standing diabetes and may result in postural hypotension, change in peripheral blood flow, exercise intolerance, enhanced intra-operative cardiovascular lability, increased incidence of asymptomatic ischaemia/myocardial infarction, decreased likelihood of survival after myocardial infarction and sudden death [66, 67]. The Steno-2 study showed that intensive multifactorial intervention can substantially reduce the incidence of abnormal autonomic function in type 2 diabetes [68]. However, whether this improvement in cardiac autonomic function independently results in a reduction in mortality is still to be determined.

Assessing Cardiovascular Autonomic Function

Although not routinely performed at an annual diabetes review, five cardiovascular autonomic function tests are widely used to assess autonomic function. These tests are non-invasive and do not require sophisticated equipment. However, these tests are considered too cumbersome to carry out in the context of a busy diabetes clinic.

Table 3.5 Reference values for cardiovascular function tests [10]

	Normal	Borderline	Abnormal
Heart rate tests			
Heart rate response to standing up (30:15 ratio)	≥1.04	1.01–1.03	≤1.00
Heart rate response to deep breathing (maximum minus minimum heart rate)	≥15 beats/min	11–14 beats/min	≤10 beats/min
Heart rate response to Valsalva manoeuvre (Valsalva ratio)	≥1.21	–	≤1.20
Blood pressure tests			
Blood pressure response to standing up (fall in systolic blood pressure (BP))	≤10 mmHg	11–29 mmHg	≥30 mmHg
Blood pressure response to sustained handgrip (increase in diastolic BP)	≥16 mmHg	11–15 mmHg	≤10 mmHg

Table 3.5 summarises the most common cardiovascular autonomic function tests [10].

Changes in Peripheral Blood Flow

Peripheral autonomic neuropathy (denervation in the periphery) can cause arterio-venous shunting, which results in increased venous pressure and hence prominent veins in the neuropathic leg/foot [15, 66] .These distended veins typically fail to collapse even when the leg is raised [15]. Leg vein oxygen tension and capillary pressure are increased in the neuropathic leg due to sympathetic denervation [16, 69]. There may be leg oedema that responds to ephedrine [17]. In the absence of peripheral vascular disease, the neuropathic foot is thus warm, and this may be one of the factors causing the osteopenia associated with the development of Charcot neuroarthropathy [14]. Peripheral autonomic neuropathy also leads to dryness of the feet as a result of decreased sweating [67].

Orthostatic (Postural) Hypotension

Orthostatic hypotension is a disabling symptom of autonomic dysfunction. Normally, a baroreflex-mediated reflex occurs in response to standing, which increases peripheral resistance, promotes venous return to the heart and increases cardiac output, thus resisting a significant fall in blood pressure. If this response fails, orthostatic hypotension and cerebral hypoperfusion occur, resulting in dizziness. It is now generally accepted that a fall in systolic blood pressure >20 mmHg is considered abnormal [70].

The symptoms of postural hypotension can be disabling for some patients who may not be able to walk for more than a few minutes. Severely affected patients are prone to unsteadiness and falls. In extreme cases, patients may be wheelchair bound as a result of very severe orthostatic hypotension. The degree of dizziness does not appear to correlate with the postural drop in blood pressure. Although the mechanisms are not fully understood, postural hypotension is undoubtedly associated with increased mortality.

The management of subjects with postural hypotension poses major problems, and for some patients there may not be any satisfactory treatment. Current treatments include the following.

- Stopping any drugs that may result in postural hypotension, such as diuretics, beta-blockers, anti-anginal agents, tricyclic agents, etc.
- Advising patients to get up from the sitting or lying position slowly, and crossing the legs.
- Increasing sodium intake up to 10 g (185 mmol) per day and fluid intake to 2.0–2.5 L/day (taking particular care in elderly patients with heart failure).
- Raising the head of the bed by 10–20° as this stimulates the renin–angiotensin–aldosterone system and results in a decrease in the nocturnal diuresis [71].
- Drinking approximately 500 mL of water stimulates a significant pressor response and improves symptoms of postural hypotension [72]. Interestingly, this pressor response can cause a systolic blood pressure increase of over 30 mmHg in some patients and is evident within 5 min of water ingestion.
- Using custom-fitted elastic stockings extending to the waist.
- Pharmacological treatment with fludrocortisone (starting at 100 μg/day). Treatment may

be limited by supine hypertension, ankle oedema and hypokalaemia; potassium supplementation is often required, particularly when higher doses are used, and it is important to monitor urea and electrolytes regularly.
- In severe cases, the following drugs may be effective: alpha-1 adrenal receptor agonist midodrine (2.5–10.0 mg tid), [73] sympathomimetic ephedrine (25 mg tid) [74] and occasionally octreotide [75] and erythropoietin (25–75 U/kg three times a week until a haematocrit level approaching normal is achieved) [76].

Gastrointestinal Autonomic Neuropathy

Damage to both extrinsic and intrinsic autonomic neurons in patients with diabetes results in symptoms of gastrointestinal dysfunction that can involve both the upper and lower gastrointestinal tract.

Gastroparesis

Autonomic neuropathy can reduce oesophageal motility, leading to dysphagia and heartburn, and can cause gastroparesis with reduced gastric emptying and swings in blood sugar [77]. The diagnosis of gastroparesis is often made on clinical grounds by evaluating symptoms (abdominal bloating, post-prandial fullness, early satiety, nausea and vomiting) and sometimes the presence of succussion splash. Barium swallow with follow through and/or gastroscopy may reveal a large food residue in the stomach. Gastric motility and emptying studies can sometimes be performed in specialised units, which may help with diagnosis.

Management of diabetic gastroparesis involves the following.

- Optimising glycaemic control, as hyperglycaemia can delay gastric emptying.
- Stopping drugs that can delay gastric emptying, such as calcium-channel blockers, the GLP-1 analogue exenatide and anti-cholinergic agents, such as antidepressants, etc.
- The use of prokinetic agents is indicated in severely affected patients. Metoclopramide at a dose of 5–20 mg orally taken before meals and at bedtime accelerates gastric emptying and also has a central anti-emetic action. Domperidone (10–20 mg tid) has central anti-emetic effects, and erythromycin (250 mg tid orally and 3 mg/kg every 8 h intravenously, i.v.) enhances the activity of the gut peptide motilin and also increases gastric emptying.
- Using anti-emetic agents as additional treatments combined with prokinetic agents (e.g. prochlorperazine 5–10 mg tid or odansetron 4–8 mg tid).
- Administering *Clostridium botulinum toxin type A* (BOTOX®; 80–200 Allergan units, injected directly into the pylorus) in cases of refractory gastroparesis. Its efficacy has been shown in open-label trials, although double-blind placebo-controlled trials have failed to demonstrate a clear benefit [78, 79].
- Using gastric electrical stimulation (GES; Fig. 3.6) as the treatment option for patients with drug refractory gastroparesis [80, 81]; this service is offered at specialist units. GES has been shown to increase the quality of life by alleviating the frequency of nausea and vomiting (Table 3.6) [80, 81].

Severe gastroparesis that causes recurrent vomiting is associated with dehydration, swings in blood sugar and weight loss, and is therefore an indication for hospital admission. The patient should be adequately hydrated with intravenous fluids and blood sugar should be stabilised by intravenous insulin. Anti-emetics could be given intravenously, and if the course of the gastroparesis is prolonged, total parenteral nutrition or feeding through a gastrostomy tube may be required (Fig. 3.7).

Autonomic Diarrhoea

Nocturnal diarrhoea is the usual presentation of autonomic involvement of the lower GI system, although some patients do present with constipation. Some patients may also have faecal incontinence. Both diarrhoea and constipation often respond to conventional treatment. Diarrhoea associated with bacterial overgrowth may respond to treatment with broad-spectrum antibiotics, such as erythromycin, tetracycline or ampicillin.

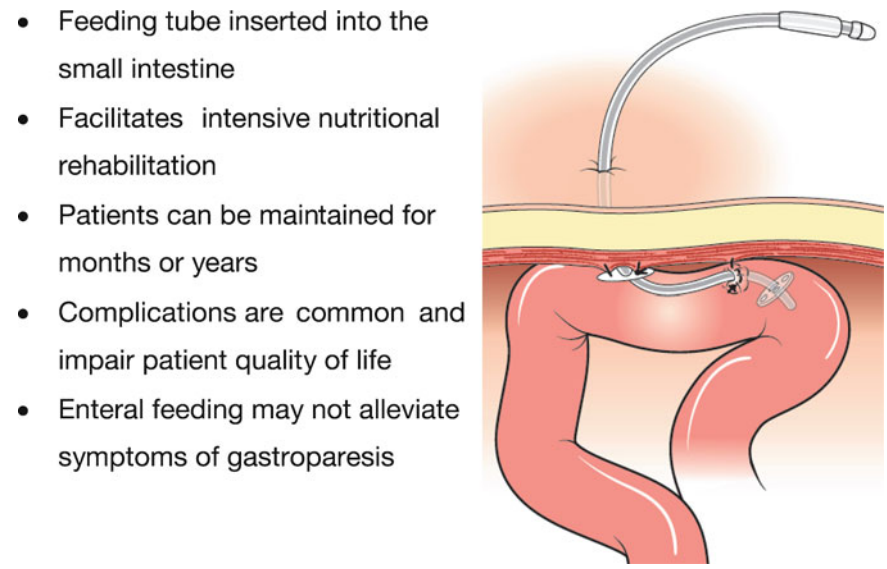

Fig. 3.6 Gastric electrical stimulation implant

Table 3.6 Impact of gastric electrical stimulation

Significantly improves
Gylcaemic control
Nausea and vomiting symptoms
Quality of life
Gastric emptying is not improved
Post-operative infection rate of 10%
Appears to be cost-effective
Further research required regarding:
Which patients are likely to respond
Optimal electrode position
Optimal stimulation parameters

Bile acid malabsorption may be treated with cholestyramine. The anti-diarrhoeal synthetic opioids (loperamide 2–4 mg qid), diphenoxylate (5 mg qid) and codeine (30 mg tid) can also be useful as they decrease peristalsis and increase rectal sphincter tone. Refractory diarrhoea may be treated with the alpha-2-adrenergic receptor agonist clonidine (doses of up to 1.2 mg/day) and the somatostatin analogue octreotide (50–75 μg bid or tid). The latter may be of benefit in refractory patients. Octreotide suppresses gastrointestinal motility, inhibits the release of motilin, serotonin and gastrin and may result in recurrent hypoglycaemia due to impaired counter-regulation.

Abnormalities of Bladder Function

Autonomic bladder dysfunction is a rare complication of autonomic neuropathy and may result in hesitancy of micturition, increased frequency of micturition and, in serious cases, urinary retention associated with overflow incontinence. Such a patient is prone to urinary tract infections. An ultrasound scan of the urinary tract and urodynamic studies may be required.

Treatments include the following.

- Mechanical methods of bladder emptying by applying supra-pubic pressure.
- The use of intermittent self-catheterisation (although the majority of patients have bacteruria, antibiotic therapy is only necessary if symptomatic urinary tract infections occur).
- Drug therapy, though seldom effective, including stimulation of muscarinic post-ganglionic receptors by parasympathomimetic drugs such as bethanechol chloride (25–100 mg qid), can enhance bladder contractility.
- Long-term indwelling catheterisation: This may be required in some cases but it does predispose patients to urinary tract infections and concurrent long-term antibiotic prophylaxis may be necessary.

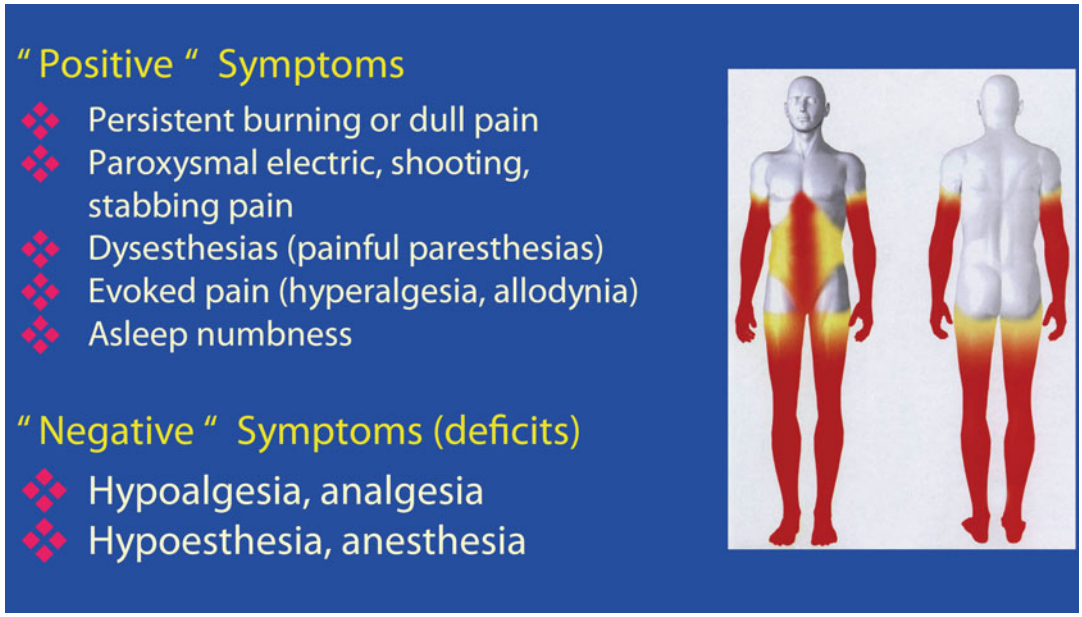

Fig. 3.7 Enteral feeding through a jejunostomy tube

Management of Gustatory Sweating

Increased sweating, usually affecting the face, and often brought about by eating (gustatory sweating) can be very embarrassing to patients. Oral anti-cholinergic agents, including oxybutynin, propantheline and glycopyrrolate, may improve symptoms [82]. However, adverse reactions, including dry mouth, constipation, potential worsening of gastroparesis and confusion, limit their use. Clonidine has also been used with some success but is also limited by side effects, including hypotension and dry mouth. Systemic side effects have led to the investigation of non-systemic approaches. Topical glycopyrrolate, a quaternary ammonium anti-muscarinic compound, has been shown to significantly decrease the incidence, severity and frequency of gustatory sweating and is well tolerated [83, 84]. Botulinum toxin has been used for gustatory sweating, though in most literature its use is limited to unilateral surgical-related cases [85].

Painful Diabetic Peripheral Neuropathy

Around half of all diabetic patients with DPN may experience painful symptoms, although many of these will not have pain of sufficient severity to warrant treatment. Of all the distressing symptoms of DPN, pain is the most prominent and most frequent reason for seeking medical attention. A definition of neuropathic pain in diabetes adapted from the original International Association for the Study of Pain's definition [86] is "pain arising as a direct consequence of abnormalities in the somatosensory system in people with diabetes". Symptoms of chronic painful DPN have been provided above and common descriptors include burning pain, "electrical shock"-type shooting pain down the legs and lancinating pain (often likened as "stabbing" or "knife-like" pains, uncomfortable tingling (paraesthesiae) and many experience contact pain for example with bedclothes at night (allodynia).

It is important to appreciate that several other conditions can masquerade as neuropathy, including entrapments, fasciitis and claudication. Neuropathic pain is also characteristically more severe at night often resulting in sleep disturbance [87] with severely affected patients complaining of being constantly tired because of severe sleep deprivation [9]. Together with painful symptoms during the day, this often leads to a reduction in individuals being able to perform

Table 3.7 Mechanisms of Neuropathic Pain (adapted from Tesfaye and Kempler 2005) [95]

Peripheral mechanisms	Central mechanisms
Changes in sodium channel distribution and expression	Central sensitisation
Changes in calcium channel distribution and expression	Aβ fibre sprouting into lamina II of the dorsal horn
Altered neuro-peptide expression	Reduced inhibition via descending pathways
Sympathetic sprouting	
Peripheral sensitisation	
Altered peripheral blood flow	
Axonal atrophy, degeneration or regeneration	
Damage to small fibres	
Glycaemic flux	

daily activities. The burden of painful DPN was reported to be considerable in one study which resulted in a persistent discomfort despite polypharmacy and high resource use, and led to limitations in daily activities and poor satisfaction with treatments that were often deemed to be inappropriate [88]. Chronic persistently painful DPN can be extremely distressing and might be associated with depression [89, 90] together with anxiety [91] and sleep loss. In one study conducted in a tertiary referral multidisciplinary clinic for painful DPN comprising patients with moderate or severe symptoms, over two-thirds were found to have anxiety and/or depression [91].

Epidemiology

Although the epidemiology and risk factors for DPN have been extensively studied [92], there are very few studies that look specifically at the prevalence of pain: the prevalence varies from 10 to 26% in a number of studies [93, 94]. In one population-based study in urban Liverpool, UK, the prevalence of painful DPN as assessed by a structured questionnaire and examination was estimated at 16% [94]. Sadly, in these patients, it was found that 12.5% had never reported their symptoms to their doctor and notably 39% had never received treatment for their pain [94]. Thus, painful DPN remains underdiagnosed and undertreated. Clearly, there is now a drive to screen all diabetic patients for neuropathy on an annual basis and to ask if they have neuropathic symptoms at the same time.

Mechanisms of Neuropathic Pain in Diabetes

The exact pathophysiological mechanisms of neuropathic pain in diabetes remain undetermined, although several mechanisms have been postulated (Table 3.7) [95]. Other potential mechanisms include the association of increased blood glucose instability in the genesis of neuropathic pain [96], an increase in peripheral nerve epineurial blood flow [97], altered foot skin microcirculation [98], reduced intra-epidermal nerve fibre density in the context of early neuropathy [99], increased thalamic vascularity [100] and autonomic dysfunction [101].

Assessment and Diagnosis of Painful DPN

The diagnosis of painful DPN in clinical practice relies on the patient's description of pain: symptoms/descriptors of DPN shown in Fig. 3.3 often associated with nocturnal exacerbation. The clinical diagnosis may be supported by nerve conduction studies and QST. Nerve conduction studies are particularly important to exclude other cases of pain, e.g. entrapment syndromes. The diagnostic criteria for DPN (possible, probable and confirmed) [1] and staging of severity are discussed above. As diabetic neuropathy is a diagnosis of exclusion, a careful clinical history and a peripheral neurological and vascular examination of the lower extremities are essential to exclude other causes of neuropathic pain and leg/foot pain, such as peripheral vascular disease,

arthritis, malignancy, alcohol abuse and spinal canal stenosis [92]. In addition, patients with asymmetrical symptoms and/or signs should be carefully assessed for other aetiologies of their symptomatology.

A number of simple numeric rating scales can be used to assess the frequency and severity of painful symptoms [102]. It is important to emphasise the difficulties in the description and assessment of painful symptoms that patients experience: pain is a very individual sensation and patients with similar pathological lesions may describe their symptoms in markedly different ways. It must also be remembered that as pain is a personal psychological experience, the external observer can play no part in its assessment or interpretation. Hence, the use of validated scales, such as the simple visual analogue style (VAS), or the numerical rating scale, such as a 11-point Likert scale (0 = no pain to 10 = worst possible pain), is recommended to assess/monitor pain intensity. Other validated scales and questionnaires, including the neuropathic pain symptom inventory [103], the modified brief pain inventory [104], the neuropathic pain questionnaire [105], the LANNS pain scale [106] and the McGill Pain Questionnaire are often used [107]. Quality of life (QoL) might be assessed by generic instruments but preferably by neuropathy-specific instruments NeuroQol [108], the Norfolk Quality of Life Scale [109] and the Neuropathic Pain Impact on Quality-of-Life questionnaire (NePIQoL) [110]. The impact of chronic pain on mood can be evaluated using scales, such as the Hospital Anxiety and Depression Scale (HADS) [111].

Management of Painful DPN

The assessment and treatment of painful DPN continues to pose a considerable challenge to clinicians, and an empathic and multidisciplinary approach is crucial as the impact of painful DPN is varied and multidimensional. Ideally, a multidisciplinary team might include input from diabetologists/endocrinologists, neurologists, the pain clinic team, specialist nurses, podiatrists, psychologists, physiotherapists and others. However, in most clinical settings, this is not possible and the management falls mainly to the diabetes physician, primary care physician or neurologist. Although there is now strong evidence implicating poor glycaemic control as a pathogenetic mechanism in the aetiology of DPN, there is no proof from randomised, controlled trials (RCTs) that this is the case for pain symptomatology. There is also evidence that vascular risk factors, such as hypertension and obesity, are risk factors for DPN [5], and so it is important to address these in the overall management of the neuropathic patient and indeed all diabetic patients.

Table 3.8 Lifestyle, metabolic control and pharmacological treatment approaches for painful diabetic peripheral neuropathy showing some of the commonly prescribed treatments

Good glucose control (HbA_{1c} 6–7%)
Lifestyle modification (diet, exercise)
Management of cardiovascular risk factors
Tricyclic antidepressants Amitriptyline, 10–75 mg/day Imipramine, 10–75 mg/day
Serotonin noradrenalin re-uptake inhibitors Duloxetine, 60–120 mg/day Venlafaxine, 150–225 mg/day
Anti-convulsants Pregabalin, 300–600 mg/day Gabapentin, 900–3600 mg/day Carbamazepine, 200–800 mg/day
Opiates Tramadol, 200–400 mg/day Oxycodone, 20–80 mg/day Morphine sulphate, SR 20–80 mg/day
Capsaicin cream (0.075%) Applied sparingly three to four times per day

DPN, diabetic peripheral neuropathy; FDA, the US Food and Drug Administration; EMA, European Medicines Agency

Pharmacological Management of Painful DPN

A large number of pharmacological treatments with known efficacy in diabetic neuropathy are listed in Table 3.8, although only two (duloxetine and pregabalin) are currently approved for the treatment of neuropathic pain in diabetes by both the Food and Drugs Administration (FDA) of the USA and the European Medicines Agency (EMA).

Tricyclic Antidepressants

Several RCTs and meta-analyses have confirmed the efficacy of the tricyclic antidepressants (TCAs) in painful DPN [112]. These agents have been shown to be effective in relieving neuropathic pain in diabetic patients. Proposed mechanisms of action include the inhibition of noradrenaline and/or serotonin re-uptake synapses of central descending pain controlled systems, and, more recently, the antagonism of *n*-methyl-D-aspartate (NMDA) receptors, which mediate hyperalgesia and allodynia. Amitriptyline and imipramine have balanced the inhibition of noradrenaline and serotonin, which may be an advantage with respect to efficacy over noradrenergic compounds, such as nortriptyline and desipramine, which on the other hand are better tolerated. In addition, drugs such as nortriptyline have less anti-cholinergic properties and have less side effects due to cholinergic blockade [113]. As the TCAs have predictable and frequent side effects including drowsiness and anticholinergic effects, it is recommended to start at a small dose especially in older patients of 10 mg/day, increasing as needed to 75 mg/day. As data from a large retrospective study of patients on TCA therapy showed an increased risk of sudden cardiac death associated with doses of >100 mg/day, caution should be taken in any patient with a history of cardiovascular disease in addition to older patients [114]. Some authorities recommend that an electrocardiogram (ECG) should be done, and if there is prolongation of the PR or QTc interval, these drugs should not be used.

Serotonin and Noradrenalin Re-uptake Inhibitors

Serotonin and noradrenalin re-uptake inhibitors (SNRIs), such as duloxetine, relieve pain by increasing the synaptic availability of 5-hydroxytryptamine (5-HT) and noradrenaline in the descending pathways that are inhibitory to pain impulses. A further advantage of duloxetine is that it has antidepressant effects in addition to the analgesic effects in diabetic neuropathy. The efficacy of this agent has been confirmed in painful DPN in several similar clinical trials at doses of 60 or 120 mg/day [115]. The pooled data from three trials confirmed that efficacy was maintained throughout the treatment period of 12 weeks, and that approximately 50% of patients had achieved at least 50% pain reduction [115]. The number needed to treat (NNT) to achieve at least 50% pain reduction (generally accepted to be clinically meaningful) was 4.9 for 120 mg/day and 5.2 for 60 mg/day [115]. An advantage of this agent is that it is not associated with weight gain. The most frequent adverse effects include nausea, somnolence, dizziness, etc. although these tend to be mild to moderate and are transient. It is recommended to start with the patient taking 30 mg of duloxetine with food once daily for 1 week and, if this is well tolerated, to increase to the effective dose of 60 mg/day.

Another SNRI, venlafaxine (dosages 150–225 mg/day), is also effective in relieving painful symptomatology [112], although cardiovascular adverse events limit its use in diabetes.

Anti-convulsants

Gabapentin and pregabalin, which bind to the α-2-δ subunit of the calcium channel, reducing calcium influx and thus resulting in reduced synaptic neurotransmitter release in the hyperexcited neurone, are the two anti-convulsants most frequently used to treat neuropathic pain [112].

The evidence for the efficacy of the first-generation agents (e.g. carbamazepine, phenytoin) is limited and mainly comes from small single-centre studies. Furthermore, these agents are associated with a relatively high frequency of adverse events, particularly central effects, such as somnolence and dizziness [112]. Gabapentin is well established as a treatment of painful DPN, although doses typically prescribed in clinical practice are much lower than the doses used in the main clinical trial of up to 3.6 g/day [116].

The other commonly used agent in this group, pregabalin, has been shown to be highly effective in the treatment of painful DPN in several RCTs [112, 117]. Based upon these and other evidence supporting its efficacy and tolerability, doses of 150–600 mg/day (in divided doses) for the treatment of diabetic neuropathic pain are recommended. The pooled analysis of seven RCTs in

painful DPN has confirmed the efficacy and safety of pregabalin [118]. Data from this pooled analysis showed an NNT of 4.04 for 600 mg/day and 5.99 for 300 mg/day. The most frequent side effects for pregabalin are dizziness, somnolence, peripheral oedema, headache and weight gain.

Local Anaesthetic/ Anti-arrhythmic Agents

The benefit of intravenous lidocaine (5 mg/kg over 30 min) in painful DPN was confirmed in a randomised, double-blind, placebo-controlled trial [118]. However, oral dosing is unavailable and ECG monitoring is necessary during administration: its use is, therefore, limited to refractory cases of painful DPN.

A multicenter, randomised, open-label, parallel-group study of lidocaine patch vs. pregabalin with a drug washout phase of up to 2 weeks and a comparative phase of 4-week treatment period showed that lidocaine was as effective as pregabalin in reducing pain and was free of side effects [119].

Opioids

Many physicians are reluctant to prescribe opioids for neuropathic pain probably because of fear of addiction. However, there is RCT evidence for some opiods, and therefore there is a good rationale for their use in the appropriate patient after the trial of first-line therapy. Of the orally administered opioids, tramadol is the best studied. It is a centrally acting synthetic opioid with an unusual mode of action, working on both opioid and mono-aminergic pathways. It has a lower abuse potential than conventional stronger opioids and development of tolerance is uncommon. In an RCT, tramadol up to 200 mg/day was effective in the management of painful DPN with a follow-up showing that symptomatic relief could be maintained for at least 6 months [120]. Finally, two randomised trials have confirmed the efficacy of controlled-release oxycodone for neuropathic pain in diabetes [121]. All studies of opioids have only assessed relatively short-term use, so the risks of tolerance and dependence in long-term usage have yet to be quantified. Thus, physicians should be aware of the potential for abuse, and should only use the opioids if other therapies have failed to provide sufficient pain relief.

Comparative ("Head to Head") and Combination Trials

A major problem in the area of the treatment of neuropathic pain in diabetes is the relative lack of comparative or combination studies. Virtually, all the trials in this review have been of active agents against placebo, whereas there is a need for more studies that compare a new or even established drug with an active comparator. A recent example of such a trial is that of Bansal et al. [122] who compared amitriptyline with pregabalin in painful DPN in a randomised, double-blind trial. This study showed that although there was little difference in efficacy pregabalin was the preferred drug because of a superior adverse event profile. Similarly, Gilron et al. studied nortriptyline and gabapentin either in combination or alone in a randomised trial and confirmed that when given together they were more efficacious than either drug given alone [123]. In a crossover study, the same group demonstrated that low-dose combination therapy with gabapentin and morphine was significantly more effective than either as mono-therapy at higher doses [124].

Topical Treatments

Topical treatments offer several theoretical advantages, including minimal side effects, lack of drug interactions and no need for dose titration. However, few have been evaluated in well-designed, randomised, control trials. See above on the use of lidocaine patch in painful DPN. Topical capsaicin works by releasing the substance "P" from nerve terminals which become depleted, and there might be worsening of neuropathic symptoms for the first few weeks of application. Topical capsaicin (0.075%) applied sparingly three to four times/day to the affected area has been found to relieve neuropathic pain [125].

Pathogenetic (Disease Modifying) Treatments

Although several disease-modifying agents are under investigation, only the antioxidant, α-lipoic acid, given intravenously is supported

by a meta-analysis and is available in certain countries [126]. Evidence supports the use of 600 mg i.v. per day over a 3-week period of this agent in reducing neuropathic pain [126]. The meta-analysis confirmed that the treatment was associated with a significant and clinically meaningful improvement in positive neuropathic symptoms as well as deficits. The results of long-term trials of oral α-lipoic acid for neuropathic symptoms and deficit are awaited.

Previous Guidelines on Treatment of Diabetic Neuropathic Pain

The European Federation of Neurological Society's (EFNS) Guidelines proposed that first-line treatments might comprise TCAs, SNRIs, gabapentin or pregabalin [127]. Most recently, the UK National Institute for Health and Clinical Excellence (NICE) published guidelines on the management of neuropathic pain in non-specialist settings [128]. While NICE ranked the level of evidence for pain outcomes with duloxetine, pregabalin and gabapentin as similar, they propose that oral duloxetine should be the first-line treatment with amitriptyline as an alternative, and pregabalin as a second-line treatment [128]. The proposal that oral duloxetine should be first-line therapy does not appear to be based upon the efficacy but rather cost-effectiveness. Finally, the American Academy of Neurology (AAN) weighted the evidence for all the clinical trials in painful DPN and recommended pregabalin as the only first-line treatment for painful DPN [129]. The panel explained that the reason for their recommendation was based on their criteria which gave pregabalin Level A evidence (defined as "established as effective"), whereas several other drugs, including gabapentin, duloxetine, venlafaxine, sodium valproate, amitriptyline, tramadol, oxycodone, apsaicin, dextromethorphan and morphine sulphate, were given Level B evidence (defined as "probably effective") [129].

Tailoring Treatment to the Patient

Initial selection of treatment is influenced by the assessment of contraindications, consideration of comorbidities and cost; for example, in diabetic patients with a history of heart disease, elderly patients on other concomitant medications such as diuretics and anti-hypertensives, patients with comorbid orthostatic hypotension and so on, TCAs have relative contraindications. In patients with liver disease, duloxetine should not be prescribed, and in those with oedema, pregabalin or gabapentin should be avoided (Table 3.9).

Table 3.9 Tailoring treatment to the patient

	Factor	Contraindication
Comorbidities	Orthostatic hypotension	TCAs
	Cardiovascular disease	TCAs
	Hepatic disease	Duloxetine
	Oedema	Pregabalin, gabapentin
	Unsteadiness and falls	TCAs
	Unsteadiness and falls	TCAs
Other factors	Weight gain	TCAs, pregabalin, gabapentin
	Cost	Duloxetine, pregabalin

Currently, the most commonly prescribed first-line agents are pregabalin, duloxetine, gabapentin and amitriptyline. A combination of these agents might be considered if there is pain, despite a change in first-line mono-therapy [130]. If pain is inadequately controlled, opioids, such as tramadol and oxycodone, might be added in a combination treatment [130].

Non-pharmacological Treatments

A full review of studies on non-pharmacological treatments for painful DPN is beyond the remit of this chapter. Unfortunately, there are few well-designed trials in this area. However, lack of efficacy and side effects from conventional drug treatments might force many sufferers to try alternative therapies, such as acupuncture [131], near-infrared phototherapy [132], low-intensity laser therapy [133], transcutaneous electrical stimulation [134], frequency-modulated electromagnetic neural stimulation (FREMS) therapy [135], high-frequency external muscle stimulation [136] and, as a last resort, the implantation of an electrical spinal cord stimulator [137].

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Clinical Examination and Risk Classification of the Diabetic Foot

4

Lawrence A. Lavery and David G. Armstrong

Abstract

Foot ulceration is one of the most common precursors to lower extremity amputations among persons with diabetes (Singh et al., JAMA. 2005; 293(2):217–28; Boulton and Vileikyte, Wounds. 2000; 12(Suppl B):12B–8; Reiber et al., Rehabil Res Dev. 2001; 38(3):309–17). Ulcerations are pivotal events in limb loss for two important reasons. They allow an avenue for infection (Armstrong and Lipsky, Diabetes Technol Ther. 2004; 6:167–77), and they can cause progressive tissue necrosis and poor wound healing in the presence of critical ischemia. Infections involving the foot rarely develop in the absence of a wound in adults with diabetes, and ulcers are the most common type of wound in this population (Armstrong and Lipsky, Diabetes Technol Ther. 2004; 6:167–77). Foot ulcers, therefore, play a central role in the causal pathway to lower extremity amputation (Pecoraro et al., Diabetes Care. 1990; 13:513–21).

The etiology of ulcerations in persons with diabetes is commonly associated with the presence of peripheral neuropathy and repetitive trauma due to normal walking activities to areas of the foot exposed to moderate or high pressure and shear forces (Armstrong et al., J Foot Ankle Surg. 1998; 37(4):303–7). Foot deformities, limited joint mobility, partial foot amputations, and other structural deformities often predispose diabetics with peripheral neuropathy to abnormal weight bearing, areas of concentrated pressure, and abnormal shear forces that significantly increase their risk of ulceration (Cavanagh et al., Diabet Med. 1996; 13 Suppl

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1:S17–22; Lavery et al., Diabetes Care. 1996; 19(8):818–21; Diabetes Care. 1995; 18(11):1460–2). Brand (The diabetic foot. In: Diabetes mellitus, theory and practice. Medical Examination) theorized that when these types of forces were applied to a discrete area over an extended period they would cause a local inflammatory response, focal tissue ischemia, tissue destruction, and ulceration. Clearly, identification of persons at risk for ulceration is of central importance in any plan for amputation prevention and diabetes care.

Keywords

Diabetic foot risk • Foot pathology • Sensory neuropathy • Tuning fork • Semmes–Weinstein monofilament • Vibration perception threshold • Modified neuropathy disability score • Limited joint mobility • Diabetic foot ulcer classification • Assessing a diabetic foot wound • Wagner ulcer classifications • UT ulcer classification

Foot ulceration is one of the most common precursors to lower extremity amputations among persons with diabetes [1–3]. Ulcerations are pivotal events in limb loss for two important reasons. They allow an avenue for infection [4], and they can cause progressive tissue necrosis and poor wound healing in the presence of critical ischemia. Infections involving the foot rarely develop in the absence of a wound in adults with diabetes, and ulcers are the most common type of wound in this population [4]. Foot ulcers, therefore, play a central role in the causal pathway to lower extremity amputation [5].

The etiology of ulcerations in persons with diabetes is commonly associated with the presence of peripheral neuropathy and repetitive trauma due to normal walking activities to areas of the foot exposed to moderate or high pressure and shear forces [6]. Foot deformities, limited joint mobility, partial foot amputations, and other structural deformities often predispose diabetics with peripheral neuropathy to abnormal weight bearing, areas of concentrated pressure, and abnormal shear forces that significantly increase their risk of ulceration [7–9]. Brand [10] theorized that when these types of forces were applied to a discrete area over an extended period they would cause a local inflammatory response, focal tissue ischemia, tissue destruction, and ulceration. Clearly, identification of persons at risk for ulceration is of central importance in any plan for amputation prevention and diabetes care.

In this chapter, we discuss the key risk factors to screen patients for foot complications. Risk factors may be broken down into four practical criterions to identify high-risk patients for ulceration and amputation. We subsequently discuss diabetic foot risk classification schemes and the two most commonly used classifications for diabetic foot ulcers.

Diabetic Foot Risk Classification

Preventing foot complications begins with identifying high-risk patients. Diabetic foot-screening programs are inexpensive and can be performed by technicians or nurses with very little training. The basics of screening involve identification of four main elements [11]: (1) history of lower extremity disease (foot ulceration, amputation, lower extremity bypass, or Charcot neuroarthropathy); (2) sensory neuropathy; (3) peripheral arterial disease; and (4) limited joint mobility or structural foot and ankle deformity.

A consensus document developed by the International Working Group on the Diabetic Foot (IWGDF) [12] is one of the most widely used systems (Table 4.1) to classify the diabetic foot. The risk of foot ulcers and amputations increased in each subsequent risk category

Table 4.1 International Working Group's diabetic foot risk classification

Risk Group 0	No neuropathy No peripheral arterial No foot deformity or limited joint mobility
Risk Group 1	Peripheral neuropathy No peripheral arterial No foot deformity or limited joint mobility
Risk Group 2	Peripheral neuropathy and foot deformity or limited joint mobility and/or Peripheral arterial disease
Risk Group 3	History of ulcer or amputation or Charcot

compared to baseline. Lavery et al. reported that a patient with neuropathy but no deformity or history of ulcer or amputation has a 1.7 times greater risk for ulceration compared with a patient without neuropathy [11]. Neuropathy with concomitant deformity or limited joint mobility yields a 12.1 times greater risk. Lastly, a patient with a history of previous ulceration or amputation has a 36.4 times greater risk for presenting with another ulcer. These risk factors compare to the first four categories in the classification system promoted by the IWGDF [13–15] (Table 4.1), and similar classification systems described by Rith-Najarian et al. [16] and Armstrong et al. [17]. Peters and Lavery [14] and Mayfield et al. [15] seem to corroborate this general line of assessment.

History of Foot Pathology

History of foot disease is the strongest predictor of ulceration and amputation. History is the least expensive screening measure [11, 18, 19]. It is the easiest risk group to identify, and the group most in need of frequent foot assessment, intensive education, therapeutic shoes, padded stockings, and rigorous blood glucose control. A current ulcer [19], past history of previous ulceration [19], or amputation [18] heightens the risk for further ulceration, infection, and subsequent amputation [5, 11, 20]. Patients in this risk group (Risk Category 3) are about 50 times more likely to have an ulcer in the next year and 36 times more likely to have an amputation compared to patients with no neuropathy or PAD (Risk Category 1) [21].

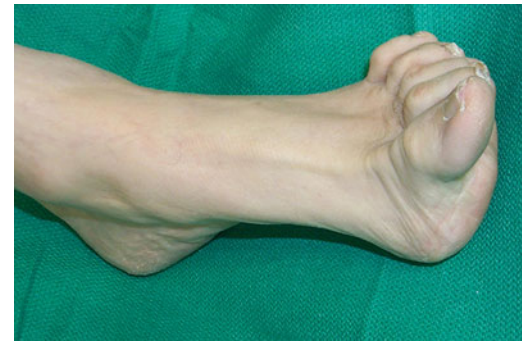

Fig. 4.1 Intrinsic muscular atrophy and foot deformity. Diabetic peripheral neuropathy also affects motor nerves, often causing atrophy of intrinsic musculature of the hand and foot. When this occurs, the extrinsic musculature work is unopposed, thus causing hammering of the toes and retrograde buckling of the metatarsal heads. Thus, both the toes (dorsally) and the metatarsal heads (plantarly) are more prominent and, therefore, more prone to neuropathic ulceration

There are several potential explanations for the increased risk. People with a history of ulceration or amputation have all the risk factors to reulcerate [12, 22]. Ulceration and amputation damage the integument and local biomechanics. After healing by secondary intention, the skin and soft tissue may be less resilient and less pliable, so they are more prone to injury. In addition, persons with a partial foot amputation often develop local foot deformities secondary to biomechanical imbalances that may cause further foci of pressure [23–25]. Structural deformities increase pressures on the sole of the foot and are associated with ulceration (Fig. 4.1). A classic example is clawing of the lesser toes and subluxation and dislocation of the metatarsophalangeal joints [25].

Sensory Neuropathy

Neuropathy is a major component of nearly all diabetic ulcerations [26]. Loss of protective sensation is a term that is often used to describe a

level of sensory loss that allows patients to jury themselves without recognizing the injury. These patients are vulnerable to physical and thermal trauma that increases the risk of foot ulceration twofold [21]. Patients with neuropathy often wear a hole in their foot much as sensate patients might wear a hole in their stocking or shoe.

Screening for neuropathy is noninvasive, fast, and inexpensive. Several consensus documents recommend that all patients with diabetes should be screened annually for sensory neuropathy [1, 27]. There are several techniques to screen for neuropathy. The absence of protective sensation may be determined using a tuning fork, a Semmes–Weinstein 10-g monofilament (SWM) nylon wire, a calibrated vibration perception threshold (VPT) meter, or a comprehensive physical examination [19].

Inspection of the feet may provide valuable clues as to the presence and severity of sensory neuropathy. Atrophy of the intrinsic muscles of the hands and feet is often a late-stage condition that is very frequently associated with polyneuropathy. When this occurs, the extrinsic muscles of the foot are unopposed, thus causing hammering of the toes and retrograde buckling of the metatarsal heads. Thus, both the toes (dorsally) and the metatarsal heads (plantarly) are more prominent and, therefore, more prone to neuropathic ulceration. This condition often leads to prominent digits and metatarsal heads, and (in the face of sensory loss) has been associated with increased risk for neuropathic ulceration. Similarly, bleeding into callus is a not an uncommon condition which is associated with neuropathy. Patients with autonomic neuropathy may present with dry skin that is poorly hydrated.

Tuning Fork

The conventional 128-Hz tuning fork is an easy and inexpensive tool to assess vibratory sensation. The test is considered positive when patients lose vibratory sensation while the examiner still perceives it [1]. The tuning fork is struck until it clangs, and the tip of the tuning fork is held against a bony prominence, such as the distal tip of the great toe. Patients are asked if they can feel the vibration. If they feel pressure but no vibration, they have loss of vibration sensation. In addition, patients should be able to feel the vibration for about 20 s. If they cannot feel the vibration for 20 s, they have abnormal vibration sensation. In addition to a standard 128-Hz tuning fork, a graduated tuning (Rydel-Seiffer) fork has provided comparable results to the vibration perception testing (r, –0.90; $P < .001$) [28, 29]. Using the graduated tuning fork, patients indicate first loss of vibration at the plantar hallux as the intersection of two virtual triangles moves on a scale exponentially from 0 to 8 in a mean (AD) of 39.8 (1) seconds [30].

Semmes–Weinstein Monofilament

The SWM is one of the most frequently utilized screening tools in the USA for identifying loss of protective sensation [1, 31]. The inability to perceive the 10-g SWM has been associated with large-fiber neuropathy [32, 33]. In three prospective studies, the 5.07 or 10-g SWM identified persons at increased risk of foot ulceration with a sensitivity of 65–91%, a specificity of 36–86%, a positive predictive value of 18–39%, and a negative predictive value of 90–95% [18, 34, 35] (Table 4.2). The SWM consists of a plastic handle supporting a nylon filament. It is portable, inexpensive, easy to use, and provides excellent negative predictive ability for the risk of ulceration and amputation [36].

There are a number of important concerns regarding the SWM. There is a wide variability in the accuracy and durability of SWM sold in the USA. Certain brands of monofilaments are more accurate than others [37]. Instruments made in the UK seem to have better initial accuracy and calibration [36]. SWMs experience material failure of the nylon monofilament and become less accurate with repeated measurements. Therefore, it is important to purchase calibrated instruments and replace them on a regular basis. In a clinical setting, it is best for the evaluator to have more than one monofilament available, as after numerous uses without a chance to "recover," the monofilament may buckle at a reduced amount of pressure, thus making it oversensitive and therefore less accurate [37].

Table 4.2 10-g Monofilament to diagnose sensory neuropathy

Study	Prevalence of ulcers (%)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Rith-Najarian [34]	11	65	86	39	95
Rith-Najarian (2000)	29	91	36	34	90
Boyko (1999)	11	68	62	18	94

Table 4.3 Results of monofilament testing with different pressure thresholds

Study	Prevalence of ulcers (%)	Sensitivity (%) Specificity (%) Positive (%)	Positive predictive value
Mueller (1989)	30	100 100	No ulcer patients felt 5.07 monofilament
Birke (1986)	100		No ulcer patients felt 6.10 monofilament
Sosenko (1990)	29	84 96 76	76%, 4.21 monofilament

Longevity and recovery testing results from an independent study suggest that each monofilament, regardless of the brand, will survive usage on approximately ten patients before needing a recovery time of 24 h before further use [31, 37]. Furthermore, differences in materials used in manufacture and environmental factors may also change the characteristics of the monofilament [37, 38].

It is clear that monofilaments should be replaced every few months to get reliable results. For instance, Booth and colleagues evaluated four brands on 10-g monofilaments. They reported that after 100 loading cycles "most" monofilaments were within 10% of the 10-g loading force. However, after 200 cycles, only 50% met that criteria.

Testing with the SWM is performed with the patient sitting supine in the examination chair with both feet level. The monofilament is applied perpendicular to the skin until it bends or buckles from the pressure. It should be left in place for approximately 1 s and then released [1]. The monofilament should be demonstrated on the patient's hand so that he/she can understand the level of pressure provided during testing. The patient should close his/her eyes for the foot examination. They should be instructed to say "yes" each time they feel the monofilament and then to identify the site where they felt the monofilament. The number of sites that should be tested with monofilaments is unclear. However, because testing is noninvasive and inexpensive, the number of sites should not be a limiting factor in testing protocols. Some authorities have recommended that measurements be taken at each of the ten sites on the foot [39]. These include the first, third, and fifth digits plantarly, the first, third, and fifth metatarsal heads plantarly, the plantar midfoot medially and laterally, the plantar heel, and the distal first interspace dorsally. However, testing just four plantar sites on the forefoot (the great toe, and base of the first, third, and fifth metatarsals) identifies 90% of patients with loss of protective sensation [40].

By convention, the 5.07 or 10-g monofilament has been commonly associated with neuropathy with loss of protective sensation. However, there are many grades of monofilaments that are available, and both lower and higher forces have been evaluated and associated with "loss of protective sensation." For instance, Sonseko and colleagues evaluated a 4.21 monofilament and found good sensitivity, specificity, and positive predictive value. Birke and colleagues evaluated the 6.10 or 60-g monofilament and found that none of the patients they evaluated could feel the monofilament (Table 4.3).

Vibration Perception Threshold Testing

A VPT meter is a semiquantitative tool to assess large-fiber neuropathy. The VPT meter (also known as biothesiometer or neurothesiometer) is a handheld device with a rubber tactor that vibrates at 100 Hz. The handheld unit is connected by an electrical cord to a base unit. This unit contains a linear scale which displays the applied voltage, ranging from 0 to 100 V (converted from microns [35, 41] (Fig. 4.2). The device is held with the tactor balanced vertically on the pulp of the toe. The voltage amplitude is then increased on the base unit until the patient can perceive a vibration. A mean of three readings (measured in Volts) is generally used to determine the VPT for each foot. "Loss of protective sensation" with VPT has commonly been considered to be about 25 V. The level of VPT testing can help to predict ulceration. In a prospective cohort study, Abbott and colleagues evaluated 1,035 patients with diabetes, no history of a foot ulcer, and a VPT greater than 25. During the follow-up period, the yearly ulcer incidence was 7.2%. For every 1 V increase in VPT, there was a 5.6% increase in the risk of foot ulceration [42].

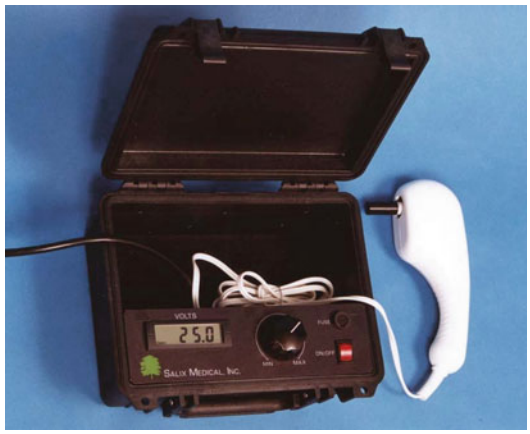

Fig. 4.2 Vibration perception threshold (VPT) meter. The vibrating tactor is placed at the distal pulp of the great toe. The amplitude (measured in volts) is increased on the base unit until the patient feels a vibration. This is termed VPT. A VPT greater than 25 V may be an optimal combination of sensitivity and specificity for identifying clinically significant loss of protective sensation using this device

VPT testing has been shown to have very good sensitivity and specificity (Table 4.4). In a prospective 4-year study, a VPT of more than 25 V had a sensitivity of 83%, a specificity of 63%, a positive likelihood ratio of 2.2, and a negative likelihood ratio of 0.27 for predicting foot ulceration [43, 44].

Modified Neuropathy Disability Score

Clinical assessment can be used to score the severity of peripheral neuropathy in order to identify high-risk patients. The Modified Neuropathy Disability Score (NDS) is a clinical assessment scoring scheme that uses standard clinical tools. These include deep tendon reflexes of Achilles tendons, vibration sensation with 128-Hz tuning fork, pinprick, and hot and cold rods. Use of these instruments, combined into a disability score, has proven to be predictive of future diabetic foot complications [19]. In a population-based prospective study, Abbot evaluated 9,710 patients with diabetes from 6 health

Table 4.4 Vibration perception threshold testing

	Prevalence of ulcers (%)	Sensitivity (%)	Specificity (%)	Positive predictive value
Sosenko (1990)	29	83	87	49%
Vileikyte (1997)	28	86	79	NS
Armstrong (1998)	33	80	85	NS

NS not stated

districts in the UK. During the 2-year follow-up period, there were 291 ulcers. Only 1.1% of patients with an NDS less than 6 developed a foot ulcer, and 6.3% of patients with NDS greater than 6 developed an ulcer [19].

Limited Joint Mobility

Neuropathy and foot deformity, when combined with repetitive or constant stress, can lead to ulceration. Characteristically, the highest plantar pressure is associated with the site of ulceration [6, 7, 45–47]. In one study of patients with peripheral neuropathy, 28% with high plantar pressure developed a foot ulcer during a 2.5-year follow-up compared with none with normal pressure [48].

Clinicians should examine the feet for structural abnormalities, including hammer or claw toes, flat feet, bunions and calluses, and reduced joint mobility to help identify pressure points that are susceptible to future ulceration. Structural deformity is frequently accompanied by limited joint mobility. Nonenzymatic glycosylation of periarticular soft tissues or tendons may contribute to limited joint motion in the person with diabetes. Neuropathy can lead to atrophy of the intrinsic muscles of the hands and feet which can cause instability at the metatarsophalangeal joint and digits [49–51]. Limitation of motion reduces the foot's ability to accommodate for ground reactive force and, therefore, increases plantar pressures [9, 52–55]. Limitation of motion of the first metatrsaophalangela joint has been defined as less than 50° of passive dorsiflexion of the hallux [11, 56] (Fig. 4.3). Additionally, glycosylation may deleteriously affect the resiliency of the Achilles tendon, thereby pulling the foot into equinus and further increasing the risk for both ulceration and Charcot arthropathy (Fig. 4.4).

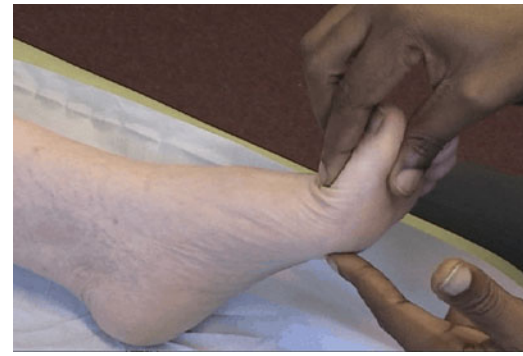

Fig. 4.3 Evaluation of first metatarsophalangeal joint dorsiflexion (limited joint mobility). Limited joint mobility is frequently encountered in patients with long-standing diabetes. This is most significant in the ankle joint (equinus) and the forefoot. Less than 50° of dorsiflexion at the first metatarsal phalangeal joint indicates clinically significant limited joint mobility

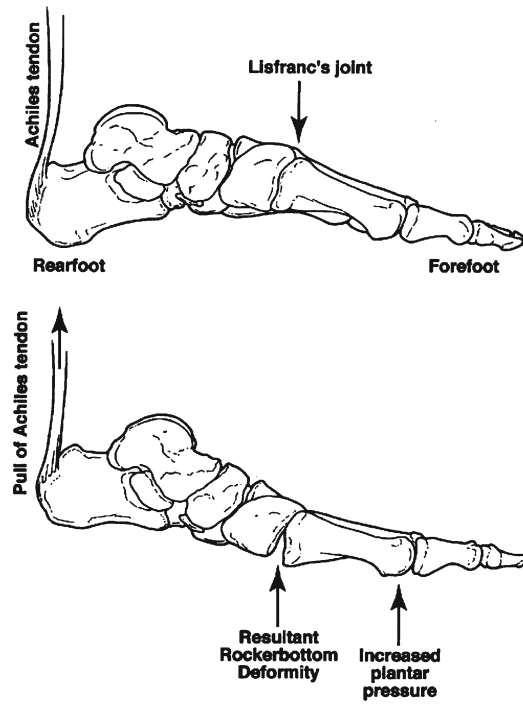

Fig. 4.4 Equinus and its relationship to elevated forefoot plantar pressure. Shortening or loss of natural extensibility of the Achilles tendon may lead to pulling of the foot into plantarflexion. This leads to increased forefoot pressure (increasing risk for plantar ulceration) and, in some patients, may be a component of midfoot collapse and Charcot arthropathy

Diabetic Foot Ulcer Classification

Foot ulcer in persons with diabetes is one of the most common precursors to lower extremity amputation. Appropriate care of the diabetic foot ulceration requires a clear, descriptive

classification system that can be used to direct therapy, communicate risk, and possibly predict outcome. Speaking a "common language" when communicating risk in the diabetic foot is, therefore, essential. This tenet is most important when treating acute diabetic sequelae, such as the diabetic wound. A classification system, if it is to be clinically useful, should be easy to use, reproducible, and effective to accurately communicate the status of wounds in persons with diabetes mellitus. There are a variety of variables that could be included in such a system, such as faulty wound healing, compliance issues, quality of wound granulation tissue, host immunity, nutritional status, and comorbidities. However, most of these variables are difficult to measure or categorize and can complicate a system, so it is not useful as a clinical tool. In contrast, three well-documented, relatively quantifiable factors associated with poor wound healing and amputation include depth of the wound [57, 58], presence of infection, and presence of ischemia [15, 59].

Seven Essential Questions to Ask When Assessing a Diabetic Foot Wound

A classification system has little value if the clinician employing it does not approach each wound in a stepwise, consistent, and logical fashion. When employing this approach, the first four questions are useful in terms of their descriptive value. The last three questions are most useful for their predictive qualities.

1. Where is the ulcer located?
   Location of a wound and its etiology go hand in hand. Generally, wounds on the medial aspect of the foot are caused by constant low pressure (e.g., tight shoes), whereas wounds on the plantar aspect of the foot are caused by repetitive moderate pressure (e.g., repetitive stress on prominent metatarsal heads during ambulation).
2. How large is the ulcer?
   Size of the wound plays a key role in determining duration to wound healing. To simplify wound diameter measurements, one may trace the wound on sterile acetate sheeting and tape this tracing into the chart (Fig. 4.5). The tracing can also be performed on the outer wrapping of an instrument sterilization pack (which would otherwise be discarded). Recently, many centers have begun employing digital photography and computer-driven planimetric wound area calculations. This provides for potentially more consistent, accurate measurements and, ultimately, for comparison of wound healing rates with other centers regionally and beyond. In an evaluation of the reproducibility of wound measurement techniques, Wunderlich and coworkers reported that wound tracing and digital planimetric assessment were by far more reliable than manual measurement of length and width [60].
3. What does the base look like?
   When describing the base of a wound, one may use terms like granular, fibrotic, or necrotic. One may record the presence or absence of any drainage, which may be described as serous or purulent, with a further description of any odor or color, as necessary.
4. What do the margins look like?
   The margins tell us a lot about the wound. If adequately debrided and off-loaded, they should be well adhered to the surface of the underlying subcuticular structures with a gentle slope toward normal epithelium. However, in the inadequately debrided, inadequately off-loaded wound, undermining of the leading edge normally predominates. This is due to the "edge effect" which dictates that an

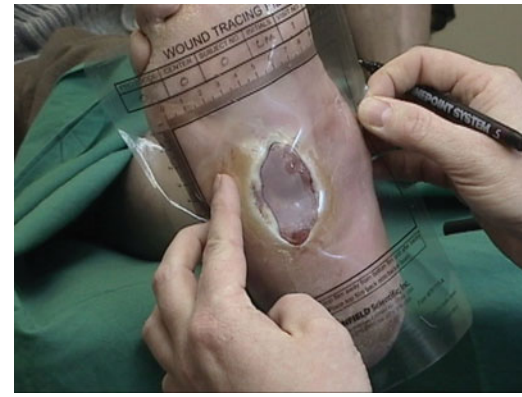

Fig. 4.5 Tracing the wound using sterile acetate sheet. Wound tracing may yield far more reproducible results in measuring wound size than simply length by width measurement

interruption in any matrix (in this case, skin) magnifies both vertical and shear stress on the edges of that interruption. This subsequently causes shearing from the underlying epithelium (making the wound larger by undermining) and increased vertical pressure (making the wound progressively deeper). If appropriately debrided and off-loaded, this effect will be mitigated. Nonetheless, the margins of the wound should be classified as undermining, adherent, macerated, and/or nonviable.

Subsequent to the first questions, which we term "descriptive," come the last three questions, which we term "classifiers." These classifiers can then be used to fit a patient into the University of Texas wound classification system. This system has evolved as a significant modification of the Wagner system to include concomitant depth, infection, and ischemia. While both systems have been shown to be predictive of poor outcomes, the UT system has been shown to be significantly more predictive and complete [61, 62]. Both, however, may be considered useful in a clinical scenario, depending on the preference of the clinician.

5. How deep is the ulceration? Are there underlying structures involved?
   These two questions are so closely related that they are combined into one. There is a possible contribution of depth to ulcer healing times [63]. Depth of the wound is the most commonly utilized descriptor in wound classification. Wounds are graded by depth. Grade 0 represents a pre- or postulcerative site. Grade 1 ulcers are superficial wounds through the epidermis or epidermis and dermis but do not penetrate to tendon, capsule, or bone. Grade 2 wounds penetrate to tendon or capsule. Grade 3 wounds penetrate to bone or into a joint. We have known for some time that wounds that penetrate to bone are frequently osteomyelitic [57]. Additionally, we have observed that morbid outcomes are intimately associated with progressive wound depth.

   Depth of the wound and involvement of underlying structures may best be appreciated through the use of a sterile blunt metallic probe. The instrument is gently inserted into the wound and the dimensions of the wound may be explored. Additionally, bony involvement is typically readily appreciable through this method.
6. Is there infection?
   The definition of bone and soft tissue infection is not an easy one. Cultures, laboratory values, and subjective symptoms are all helpful. However, the diagnosis of an infection's genesis and resolution has been and continues to be a clinical one. While criteria for infection may be something less than clear-cut, there is little question that the presence of infection is a prime cause of lower extremity morbidity and frequently eventuates into wet gangrene and subsequent amputation. Therefore, in an effort to facilitate communication and effect consistent results, the foot care team should agree on the criteria for this very important risk factor.
7. Is there ischemia?
   As discussed above, identification of ischemia is of utmost importance when evaluating a wound. Ischemic wounds were found to take longer to heal compared to neuropathic wounds without deformities [63]. If pulses are not palpable or if a wound is sluggish to heal even in the face of appropriate off-loading and local wound care, noninvasive vascular studies are warranted followed by a prompt vascular surgery consultation and possible intervention to improve perfusion.

Wagner Ulcer Classifications

Several diabetic classification systems have been reported in the medical literature. This section aims to chronologically review some of the most commonly described classification systems currently used by a variety of practitioners to stage diabetic foot wounds and to discuss outcomes related to their use. One of the most frequently cited diabetic wound classification systems was first described by Meggitt [64] in 1976 and Wagner [65] in 1981. The system is based mainly on wound depth and consists of six wound grades. These include Grade 0 (intact skin), Grade 1 ("superficial ulcer"), Grade 2 (deep ulcer to tendon, bone, or joint), Grade 3 (deep ulcer with abscess or osteomyelitis), Grade 4 ("forefoot

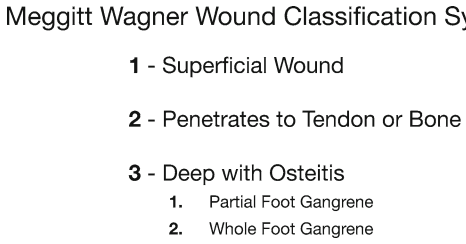

Fig. 4.6 Meggitt–Wagner wound classification system

gangrene"), and Grade 5 ("whole-foot gangrene"). This classification is outlined in Fig. 4.6.

The classification system contains three key descriptors, including depth, infection, and ischemia. However, it does not consistently include these important risk factors in every ulcer grade. Infection is included in only one of the six Wagner ulcer grades, and vascular disease is only included in the last two classification grades. The first three grades are concerned only with depth. It is perhaps for this reason that they are the most commonly used, whereas the last three are largely ignored because of their limited clinical use. The descriptors Meggit and Wagner used for ischemia were forefoot and whole-foot gangrene. These represent the most severe form of end-stage disease, and therefore cannot help to guide proactive interventional therapy, except frank ablation of the affected site. In addition, because gangrene can be caused by infection, it may not always have a vascular origin. Since there are better diagnostic tools to assess and treat PAD, more robust criteria for ischemia will improve diagnosis, interventions, and amputation prevention.

There are several papers that have attempted to validate the Wagner classification system [66, 67]. Calhoun et al. [67] evaluated wounds that were infected and retrospectively assigned Wagner grades to them. They found that when wounds were treated according to what they considered a healthy standard of care, then success, which they defined as eradication of infection and prevention of readmission for 1 year, was frequently achieved despite wound grade [67]. Van Acker [68] found the Wagner classification to have significant association with the duration of healing of the ulcer. Armstrong et al. [62] suggested that patients with Wagner stages 4 and 5 may be grouped together as the two groups did not have separate prognostic value. In addition, these patients are often referred directly to a surgeon for amputation and are rarely seen by the diabetic foot team. The system was adapted to combine medical and surgical elements of therapy to monitor the treatment of diabetic foot infection. Unfortunately, in requiring that wounds be infected as an inclusion criterion, it made assessment of this classification problematic, as Wagner wound grades 0–2 classically have no infection descriptor attached to them. In fact, the only mention of infection in this system occurs in Grade 3. It is this fact that causes many to customize this system such that it often takes on distinctly different regional characteristics. This unfortunately limits its usefulness as a standard diabetic foot classification.

In the 1980s and 1990s, many authors, including Forrest and Gamborg-Nelson [69], Pecoraro and Reiber [70], Arlt and Protze [71], and Knighton et al. [72], proposed their own wound classifications; however, these systems have not gained universal acceptance. More recent classification systems that have been proposed include the UT classification modification by Armstrong and Peters [63], the PEDIS system by IWGDF members [73], and the S(AD) SAD system proposed by Macfarlane and Jeffcoate [74, 75]. These systems will require validation and to gain universal acceptance.

UT Ulcer Classification

The University of Texas Health Science Center in San Antonio (UT) proposed a classification that included depth, infection, and vascular status in 1996 [62, 76]. The classification integrates a system of wound grade and stage to categorize wounds by severity. It is based around two fundamental questions the clinician asks when assessing a wound: (1) How deep is the wound? and (2) Is the wound infected, ischemic, or both? The classification formulates into a matrix with infection and/or ischemia as the vertical axis and depth as the longitudinal axis. This system is illustrated in Fig. 4.7.

Scale	Grade 0	Grade 1	Grade 2	Grade 3
A	Pre or postulcerative lesion completely epithelialized	Superficial wound, not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
B	with infection	with infection	with infection	with infection
C	with ischemia	with ischemia	with ischemia	with ischemia
D	with infection and ischemia	with infection and ischemia	with infection and ischemia	with infection and ischemia

Fig. 4.7 University of Texas wound classification system

Similar to other wound classification systems, the UT system grades wounds by depth. Grade 0 represents a pre- or postulcerative site. Grade 1 ulcers are superficial wounds through either the epidermis or the epidermis and dermis but do not penetrate to tendon, capsule, or bone. Grade 2 wounds penetrate to tendon or capsule, but the bone and joints are not involved. Grade 3 wounds penetrate to bone or into a joint. Within each wound grade, there are four stages: clean wounds (A), nonischemic infected wounds (B), ischemic wounds (C), and infected ischemic wounds (D).

The Grade 0 wound: Grade 0 wounds are preulcerative areas or previous ulcer sites that are now completely epithelialized after debridement of hyperkeratosis and nonviable tissue. The diagnosis of a Grade 0 wound can be made only after removal of any regional hyperkeratosis, as quite often frank ulcerations may be hidden by overlying calluses. The Grade 0-A wound is then a preulcerative area or a completely epithelialized postulcerative are. The Grade 0-B wound is a 0-A lesion with associated cellulitis. The Grade 0-C wound is a 0-A lesion with concomitant regional signs of ischemia. The Grade 0-D wound is a 0-B lesion coupled with a working diagnosis of lower extremity ischemia as defined above.

Although lesions that fall into the Grade 0 category do not have a break in the epidermis and may not be classically classified as "wounds," the category is important in the identification of sites that are "at risk" for future ulceration and to monitor and prevent reulceration of newly healed wounds. Because there is a very high rate of reulceration (28–50%) [12], the Grade 0 classification allows physicians to follow the progression of wounds over time from healed to reulcerated.

The Grade I wound: Grade I wounds are superficial in nature. They may be either partial or full-thickness skin wounds without the involvement of tendon, capsule, or bone. The Grade I-A wound is, therefore, superficial, partial, or full-thickness wound. The Grade I-B wound is an infected superficial wound. As with any neuropathic lesion, Grade I-B wounds should be examined very carefully. By definition, the Grade I-B wound implies superficial infection without the involvement of underlying structures. If the wound shows signs of significant purulence or fluctuance, further exploration to expose a higher grade infection is in order. The Grade I-C wound is I-A plus vascular compromise and the Grade I-D wound is the infected I-B wound with concomitant ischemia.

The Grade II wound: Grade II wounds probe deeper than the Grade I wounds. Grade II wounds may involve tendon or joint capsule but not bone. The reason for the distinct delineation between wounds that probe to bone and those without bone or joint involvement is because of the high correlation between probing to bone and osteomyelitis (Lavery, 2005 #11205) [57, 77].

The II-A wound may, therefore, probe to tendon or joint capsule, but not bone. The II-B wound is II-A plus infection, and again the bone and joint are not involved. The Grade II-C wound is II-A plus ischemia, and the Grade II-D wound corresponds to II-B plus ischemia.

The Grade III wound: A wound that probes to bone is categorized as a grade III wound. The modifiers are then added pending the presence of comorbid factor. The III-A wound probes to bone without local or systemic signs of acute infection. The III-B wound probes to bone with signs of acute infection. The III-C wound is identical to III-A with concomitant ischemia. The III-D wound is characterized by active infection, exposed bone, and vascular insufficiency.

The criterion for each of the stages is based on clinical and laboratory data. The working diagnosis of lower extremity ischemia may be based on clinical signs and symptoms, such as absence of pedal hair, absent pulses, claudication, rest pain, atrophic integument, dependent rubor or pallor on elevation, plus one or more of the noninvasive criteria (transcutaneous oxygen measurements of <40 mmHg, ankle-brachial index of <0.80, or absolute toe systolic pressure <45 mmHg) [78–82].

Clean ulcers may be defined as wounds without local or systemic signs of infection. The clinical diagnosis of infection in persons with diabetes is often difficult and defined by narrow, subtle parameters. Wounds with frank purulence and/or two or more of the following local signs may be classified as "infected": warmth, erythema, lymphangitis, lymphadenopathy, edema, pain, and loss of function. Systemic signs of infection may include fever, chills, nausea, vomiting, or generalized malaise [83]. This clinical diagnosis of infection is often obscured by neuropathy and possibly immunopathy. In the insensitive foot, pain and/or loss of function are poor indicators of inflammation and infection [84]. Likewise, diabetic subjects have been shown to posses deficiencies in leukocyte adherence, chemotaxis, phagocytosis, and diapedesis [85–87] and often do not have leukocytosis in the presence of acute soft tissue or bone infection [84, 88, 89]. Warmth and edema are less than ideal indicators of infection, as ulcerated sites tend to be warmer and more edematous than the corresponding site contralaterally regardless of the presence of infectious disease [90]. However, despite these impediments, diagnosis of a diabetic foot infection remains primarily a clinical one [88, 89]. The diagnosis and subsequent treatment of infection may also be assisted by laboratory studies, positive deep tissue cultures, or wound-based curettage [91]. When osteomyelitis is suspected, bone biopsy with appropriate pathology and culture studies is still the gold standard for diagnosis.

Armstrong et al. validated the predictive value of the UT classification system in 1998 [62] and noted a significant overall trend toward an increased prevalence of amputations as wounds increased in both grade (depth) and stage (comorbidity). For example, patients whose wounds were both infected and ischemic were noted to be almost 90 times more likely to receive a high-level amputation compared with patients in a less advanced wound stage, and patients whose wound probed to the underlying bone were over 11 times as likely to receive a high-level amputation [63]. Unfortunately, the study was retrospective and was not a multicenter trial. In addition, some degree of bias may have been present since the study was carried out by the center that first described the system and the clinicians using it that are intimately familiar with the system.

Oyibo et al. [92] compared the Wagner classification system with the UT system in a multicenter, prospective, longitudinal, case–control study of 194 patients. The study suggested that both the UT and the Wagner classification system correlated similarly with clinical outcome. Both systems associated higher grades with a greater likelihood of an ulcer not healing and a greater chance of limb amputation [63]. The trend for grade of the UT classification system was slightly more robust than the trend for grade of the Wagner classification. The inclusion of comorbid factors, such as infection and/or ischemia, to grade (depth) when classifying an ulcer with the UT system improves description and adds to the predictive power of a wound classification system, especially for ulcers within the same grade level but at a different stage. Based on this, the UT

wound classification showed promise as a more practical system.

As with other classification systems, the UT classification is not void of potential shortcomings. Neuropathy, considered by many to be an important etiologic and prognostic factor, is not included in the UT classification system. This exclusion is based on the argument that neuropathy is a preexisting condition in most diabetic foot wounds and it is not a significant independent risk factor. The UT classification system also does not describe the anatomic region of the wound: however, it is still not clear that anatomic is a factor that would either change treatment or clinical outcomes. Another shortcoming of the UT classification system is that it leaves no room for more specificity or complexity. Simplicity is one reason that the Wagner classification has remained popular. The UT classification is already fairly complex with four-by-four matrix-grading system. Additional information that is not strongly associated with triggering a change in treatment could hinder the practical application of wound classification.

All the proposed classification systems have attempted to integrate local factors with varying degrees of validated success. These systems might be viewed with the same considerations we use when we think of a language. A universal idiom has dialects, accents, and pragmatic slang. Different exposure and usage of the language will cause it to change over time. These dialects should be judged in light of a progress toward a lower global prevalence of lower extremity amputations. To avoid inconsistencies, we need to move toward a validated and universally accepted diabetic foot wound classification system.

In conclusion, it is observed that many of the most common component causes for neuropathic ulceration, infection, and subsequent amputation may be identified using simple, inexpensive equipment in a primary care setting. A consistent, thoughtful assessment of the diabetic foot is pivotal to identify high-risk patients. Subsequent to the gathering of clinical data through sequential assessment, appropriate classification of the wound becomes paramount in our efforts to document and communicate the level of risk to all members of the health care team caring for the person with diabetes. These simple approaches should improve communication and facilitate amputation prevention.

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Clinical Features and Diagnosis of Peripheral Arterial Disease

5

Cameron M. Akbari

Abstract

Peripheral arterial disease is a fundamental consideration in the patient presenting with a diabetic foot. Although broad in context, it is only part of the overall alteration in vascular structure and function characterized by two distinct pathologic processes: a nonocclusive microcirculatory impairment involving the capillaries and arterioles of the kidneys, retina, and peripheral nerves and a macroangiopathy manifesting as atherosclerotic lesions of the coronary and peripheral arterial circulation. The former is relatively unique to diabetes and is best described as an accelerated microangiopathy rather than an occlusive process. In addition to its well-recognized contribution to the development of diabetic neuropathy, retinopathy, and nephropathy, this microvascular dysfunction is also of paramount importance in the diabetic foot.

Keywords

Peripheral arterial disease • Diabetic limb salvage • Foot ulceration • Noninvasive arterial testing • Doppler segmental pressures • Toe pressures • Doppler waveform analysis • Pulsed volume recordings • Duplex ultrasound • Transcutaneous oxygen tension • TcPO2 • Laser Doppler perfusion • Invasive arterial testing • Arteriography

Pathogenesis and Clinical Features

Peripheral arterial disease is a fundamental consideration in the patient presenting with a diabetic foot. Although broad in context, it is only part of the overall alteration in vascular structure and function characterized by two distinct pathologic processes: a nonocclusive microcirculatory impairment involving the capillaries and arterioles of the kidneys, retina, and peripheral nerves and a macroangiopathy manifesting as atherosclerotic lesions of the coronary and peripheral arterial circulation. The former is relatively unique to diabetes and is best described as an accelerated microangiopathy rather than an occlusive process. In addition to its

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well-recognized contribution to the development of diabetic neuropathy, retinopathy, and nephropathy, this microvascular dysfunction is also of paramount importance in the diabetic foot. Described in detail elsewhere in this book, microvascular disease in the diabetic foot must be considered in any discussion on peripheral arterial disease in diabetes, since its presence modifies conventional concepts of critical limb ischemia and healing. Indeed, because of the unique biologic milieu of the diabetic foot and owing to the combined roles of neuropathy and microneurovascular dysfunction, even a moderate degree of ischemia will lead to ulceration, progressive tissue loss, and failure to heal [1–7].

In contrast to the unique microvascular alterations, the macroangiopathy of diabetes is morphologically and functionally similar to that occurring in the nondiabetic population, and is due to atherosclerotic occlusive disease. Multiple epidemiological studies spanning several decades have clearly established the link between diabetes and vascular disease. The Framingham Study of over 5,000 subjects demonstrated that diabetes is a powerful risk factor for atherosclerotic coronary and peripheral arterial disease, independent of other atherogenic risk factors, with a relative risk averaging twofold in men and threefold for women. Moreover, the risk of stroke is at least 2.5-fold higher in patients with diabetes, and other studies have confirmed that diabetes is strongly associated with atherosclerosis of the extracranial internal carotid artery. Along the spectrum of lower extremity arterial occlusive disease, the association with diabetes becomes even greater. Compared to the nondiabetic patient, peripheral arterial disease presents at least a decade earlier in the diabetic patient. More specifically with respect to symptoms, the prevalence of intermittent claudication is at least two to four times higher among patients with diabetes, and, among all other cardiovascular risk factors, diabetes continues to impart the strongest association for the development of critical limb ischemia [8–11].

Unfortunately, the diabetic patient often presents with additional atherogenic risk factors; the presence of these is more than additive. For example, the risk for the development of critical limb ischemia increases fourfold in the diabetic patient, threefold in the nondiabetic smoker, and twofold in the nondiabetic patient with hyperlipidemia [12]. When one considers the concomitance of cigarette smoking and hypercholesterolemia in the diabetic patient, the need for modifiable risk factor reduction to prevent limb loss becomes compelling.

As noted above, atherosclerotic disease is the pathologic cause of lower extremity occlusive disease in both diabetic and nondiabetic patient; however, the major differences between these two populations of patients are the pattern and location of the occlusive lesions. Whereas occlusive lesions of the superficial femoral and popliteal segment are commonly found in the nondiabetic patient with limb ischemia, the classic anatomic location of atherosclerotic lower extremity disease in the diabetic patient is the infrageniculate, or tibial, arteries [13] (Fig. 5.1). Indeed, in the presence of diabetes and its associated microangiopathy and neuropathy, this "single-level" disease is profound enough to cause ulceration and impair healing. However, the foot arteries are almost invariably patent, which allows for successful distal arterial reconstruction despite extensive, more proximal tibial arterial disease (Fig. 5.2). Atherosclerosis involving the femoro-popliteal and/or the aorto-iliac segment (the so-called multilevel disease) is also found on occasion, especially in the diabetic patient with a significant smoking history.

Diagnosis

Assessment of the arterial circulation represents the cornerstone of the overall treatment algorithm for diabetic limb salvage. Advances in the surgical treatment of diabetic arterial occlusive disease, particularly the use of paramalleolar bypass grafting and refined techniques in percutaneous endovascular intervention, have markedly decreased the number of patients previously deemed "inoperable," thereby highlighting the importance *of early and accurate* diagnosis in the diabetic foot with suspected ischemia. Indeed, many failures of limb salvage may be attributed to the delay in

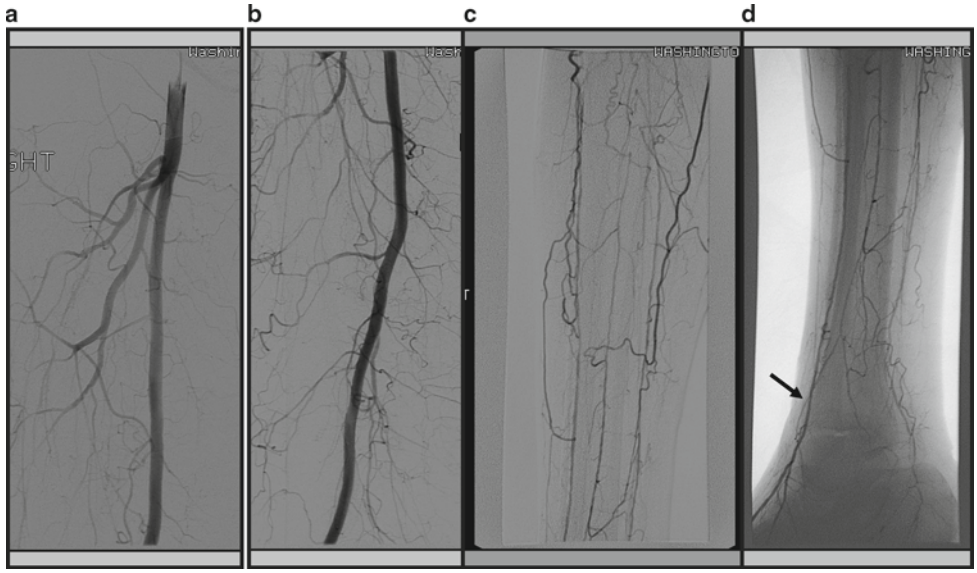

Fig. 5.1 Arteriogram of a diabetic patient presenting with a nonhealing hallux ulcer. Note the normal femoral–popliteal segment (**a**, **b**) with severe tibial occlusive disease (**c**) and reconstitution of the distal anterior tibial artery and dorsalis pedis artery (*arrow*, **d**)

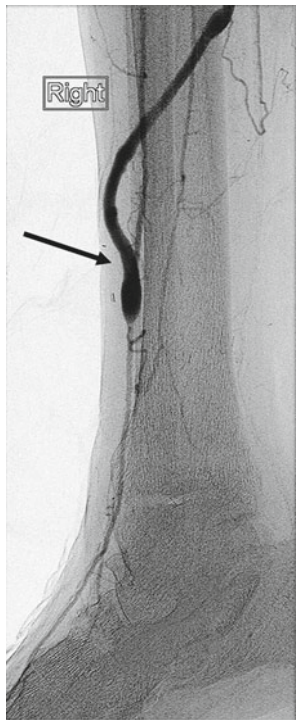

Fig. 5.2 Arteriogram of the same patient from Fig. 5.1, taken 2 years after popliteal to distal anterior tibial artery bypass, showing a widely patent bypass graft (*arrow*)

diagnosing (and treating) arterial insufficiency, and when one considers the subsequent social, medical, and legal ramifications resulting thereof, it is clear that the burden falls on the practicing podiatrist, surgeon, and/or internist to accurately assess the arterial circulation. Critical to this is an orderly approach, starting with the time-honored history and physical exam, followed by *selective* use of the vascular diagnostic laboratory, which assumes an understanding of the technique and limitations of noninvasive arterial tests in the diabetic patient.

History and Physical Examination

Any patient presenting with a foot ulceration or gangrene should immediately arouse suspicion of underlying arterial insufficiency, even if it has already been categorized as a "neuropathic" or "infected" ulcer. The history of the ulceration may provide several clues: What is the duration? (A long-standing, nonhealing ulcer is suggestive of coexisting ischemia.) Has the patient healed other ulcers on that foot? Did the present ulcer

heal previously? Other useful information might include a history of previous revascularization (including the contralateral leg), other cardiovascular events, and coexisting cardiovascular risk factors.

Although claudication or rest pain has traditionally been associated with vascular disease, it is important to recognize that its absence in the diabetic patient certainly does not rule out ischemia for several reasons. First, associated sensory neuropathy may obscure or mask those symptoms. Secondly, the classic pattern of diabetic atherosclerosis, with sparing of the iliac and femoral–popliteal arteries, may not result in classic calf or thigh claudication. Finally, and most importantly as emphasized here and elsewhere, only a *moderate* degree of arterial insufficiency will lead to ulceration and prevent healing of ulcers in the complex physiologic milieu of the diabetic foot; such a degree of ischemia may not result in ischemic rest pain symptoms.

A focused physical exam will yield helpful information about underlying arterial disease in the diabetic patient with foot ulceration. Mere inspection of the leg and foot, including the ulcer, will often provide suggestive clues. For example, a distal ulceration (on the tip of a digit), an ulceration unassociated with an exostosis or weight-bearing area, and the presence of gangrene are all strongly consistent with underlying ischemia. Lack of bleeding with debridement of the ulcer should immediately raise concern for underlying arterial insufficiency. Other signs suggestive of ischemia include pallor with elevation, fissures, particularly at the heel, and absent hair growth. Although poor skin condition and hyperkeratosis may not always be good indicators of arterial disease, they should be noted, as they may help confirm initial clinical impressions.

The pulse examination, including the status of the foot pulses, is the single most important component of the physical exam, and is incorporated in every single algorithm of diabetic foot management. Fundamentally, as has been emphasized, *ischemia is always presumed to be present in the absence of a palpable pulse*.

Although not difficult, an accurate pulse examination of the lower extremities is an acquired skill, and time should be devoted to practicing and perfecting the technique. The femoral pulse is palpated midway between the superior iliac spine and the pubic tubercle, just below the inguinal ligament. The popliteal pulse should be palpated with both hands and with the knee flexed no more than 15° (Fig. 5.3).

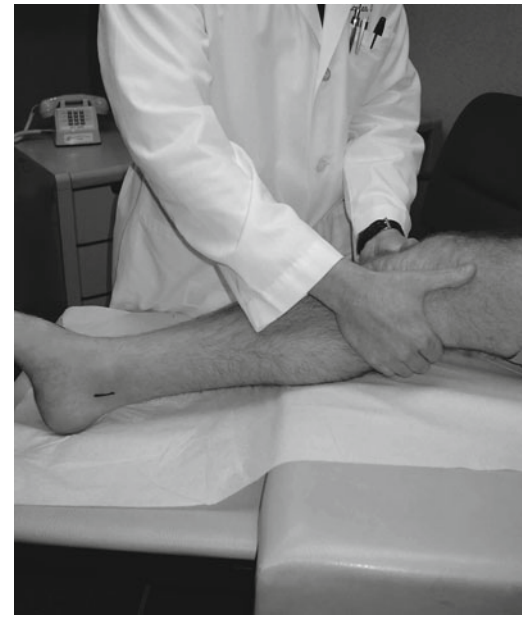

Fig. 5.3 Palpation of the popliteal pulse

Great attention should be directed toward the foot pulses, which requires a knowledge of the usual location of the native arteries. The dorsalis pedis (DP) artery is located between the first and second metatarsal bones, just lateral to the extensor hallucis longus tendon, and its pulse is palpated by the pads of the fingers as the hand is partially wrapped around the foot (Fig. 5.4a). If the pulse cannot be palpated, the fingers may be moved a few millimeters in each direction, as the artery may have an occasional slight aberrant course. A common mistake is to place a single finger at one location on the dorsum of the foot. The posterior tibial (PT) artery is typically located in the hollow just behind the medial malleolus, approximately halfway between the malleolus and the Achilles tendon. The examiner's hand should be contralateral to the examined foot (i.e., the right hand should be used to palpate the left foot and vice versa) so as to allow the hand curvature to follow the ankle (Fig. 5.4b).

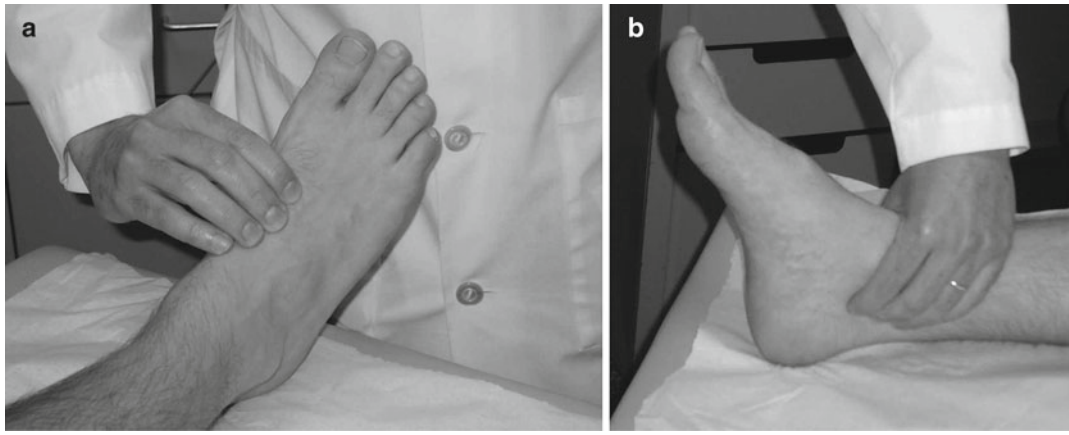

Fig. 5.4 Palpation of the dorsalis pedis (**a**) and posterior tibial (**b**) artery pulses. Note that the examiner's left hand is used to palpate the right posterior tibial artery pulse, allowing the hand to cradle over the top of the ankle

Noninvasive Arterial Testing

The clinician caring for the diabetic foot is faced with the comparable challenges of deciding if and when to order noninvasive arterial tests, which tests to order, and how to interpret them; unfortunately, the confusion surrounding this very issue often leads to delays in diagnosis and treatment. Moreover, all of the presently available tests have significant limitations in the presence of diabetes (as discussed below), and misinterpretation of their results may lead to further delays and errors in diagnosis. It is, therefore, essential that the clinician gain a thorough familiarity with the tests, recognition of each test's limitations, and an understanding that the vascular lab is complementary to, and not a substitute for, the bedside evaluation.

Doppler Segmental Pressures

The use of segmental pressures is based on the principle that arterial stenosis or occlusion will result in a decrease (or "drop-off") in the pressures measured distal to that lesion. For example, an iliac stenosis will result in diminished pressures at the thigh level (and distally as well), whereas a femoral or popliteal lesion will yield lower pressures at the ankle. By measuring the pressures at multiple sites (high thigh, low thigh, calf, and ankle), the disease may be localized to the intervening segment, where a drop-off in pressure occurs. Additionally, the pressure at a particular site (e.g., ankle) is compared to a reference pressure (usually, the highest arm pressure), yielding a ratio, such as the ankle brachial index (ABI).

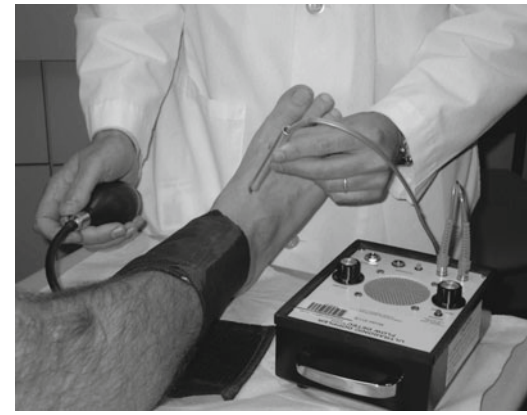

Fig. 5.5 Measurement of the ankle pressure

The technique of measuring the ABI involves the use of appropriately sized cuffs (placed at the ankle) and a specialized sensor (usually, a handheld Doppler device) to detect systolic flow at the dorsalis pedis and posterior tibial arteries (Fig. 5.5).

Arm pressures are measured bilaterally first using the Doppler (and not the stethoscope) at the

brachial artery. The lower extremities are then examined, and the Doppler is used to detect flow at the DP and PT arteries. The ankle cuff is inflated until no flow is heard; subsequently, it is deflated and the pressure is recorded as that pressure at which the first audible Doppler signal is heard. The ABI is then calculated using both the dorsalis pedis and posterior tibial measurements. Because the systolic pressure increases toward the periphery (due to reflections from branch points and bifurcations, which amplify the systolic pressure), the ankle pressure is normally greater than the brachial pressure, and a "normal" ABI is 1.0–1.2.

By placing the cuff more proximally (such as on the thigh) while insonating the DP and PT arteries, the pressure at that segment (e.g., thigh pressure) may be obtained. Normally, thigh pressures are at least 30 mmHg greater than arm pressures due to girth considerations, and lesser values are consistent with iliac and/or proximal femoral arterial disease.

The limitation of Doppler segmental pressures (ABIs) in the diabetic patient is well recognized and is due to the frequent occurrence of medial arterial calcification in the diabetic limb. Its presence can result in noncompressible arteries with artifactually high systolic pressures and inaccurate ABIs. Therefore, a "normal" ABI in a patient with diabetes should be interpreted with caution. Measurements may also be affected by inappropriately sized cuffs. For example, too narrow a cuff will result in artifactually high pressures, and the so-called narrow cuff artifact is often associated with obese patients. A good rule of thumb is that the width of the cuff should be approximately 1.2–1.5 times the diameter of the limb that it encircles.

Despite these limitations, ABIs are an important component of the physical exam and should be measured in every patient with a diabetic foot ulcer, as their specificity (i.e., a low ABI) is helpful in confirming the presence of arterial insufficiency. However, it should *never* be used to predict healing potential; furthermore, a diabetic foot with nonpalpable pedal pulses and a "normal" ABI should *not* be dismissed as having normal arterial circulation.

Toe Pressures

Support for the use of toe pressures comes from several studies showing lower levels of calcification in the toe vessels of diabetic patients, and therefore these measurements are less likely to be artifactually elevated. The technique is similar to that used for segmental pressures, and involves a digit cuff (usually, 2–3 cm) placed at the base of the first toe (Fig. 5.6a). Because a greater sensitivity is required, a plethysmograph (to detect volume-dependent pulsation) is used instead of a Doppler, and the cuff is deflated until the first pulsation is recorded on the strip paper (Fig. 5.6b). The pressure at which the pulsation returns is the toe pressure, and this may be compared with the brachial measurement to yield a toe brachial index (or TBI). Normally, toe pressures are 60–80% of the arm pressure (i.e., a TBI of 0.6–0.8) and lower values suggest lower extremity arterial occlusive disease at some level.

Despite its advantages in the presence of calcified vessels, toe pressure measurements also have several limitations. The presence of a bandage or toe ulcer often precludes placement of the cuff. In addition, since a plethysmograph is used to detect the pressure at which volume increases, the quality of the tracing may be affected by any vasoconstricted state (e.g., cold weather, cold room, nervous patient, etc.). Finally, both the volume and photo plethysmographs require close calibration, and poor contact of the photocell with the skin yields poor results.

Doppler Waveform Analysis

The Doppler effect refers to the shift in frequency as a transmitted sound wave is reflected from a moving target (such as a red cell). Clinically, these shifts in frequency indicate the direction of flow, depending on whether the reflected frequency is higher or lower than the transmitted frequency. Normal arterial pulsatile flow is characterized by three distinct phases with each cardiac cycle: (a) forward flow during systole (due to myocardial contraction); (b) reversal of flow

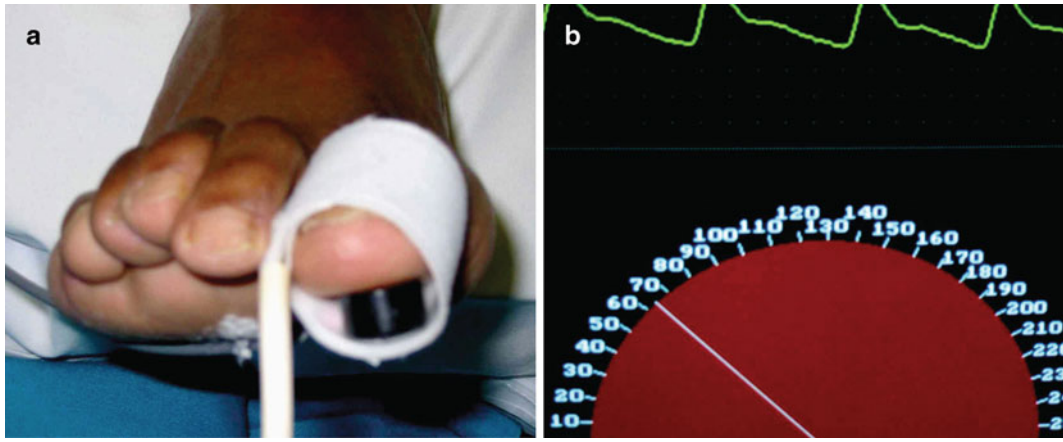

Fig. 5.6 Toe pressures being measured using air plethysmography. (**a**) The plethysmograph probe is seen (indicated by the broken *arrow*). The cuff is deflated and the pressure at which until the volume-dependent pulsation returns (indicated by the *solid arrow* in **b**) is the toe pressure

during early diastole (due to an increase in peripheral resistance which causes a reflection of the wave); and (c) forward flow in late diastole (as the reflected wave hits the next oncoming wave). An analogy would be a hand dropping a ball onto the floor: initially, it will drop down (forward flow), and then as it hits the floor (resistance), the ball will travel back up (reversal flow). Finally, it will hit the hand again and travel back toward the floor (late forward flow). Because the Doppler shift characterizes changes in the direction of flow, the normal arterial flow pattern is described as being "triphasic" by Doppler examination. With a proximal arterial stenosis or occlusion, the waveform loses several of its characteristics. The systolic peak becomes blunted, and there is loss of the reverse-flow component during diastole, resulting in a "monophasic" waveform. (The loss of the reverse-flow component is due to a *decrease* in the peripheral resistance beyond the stenosis as a result of relative ischemia distal to the arterial stenosis. The ischemia induces vasodilation in the distal arterial bed.)

Clinically, the technique involves the use of a continuous-wave 8–10 MHz Doppler probe which insonates the femoral, popliteal, dorsalis pedis, and posterior tibial arteries. The signal is then processed onto a strip chart recorder and analyzed. Alternatively, the signal may be processed by a more sensitive method called spectral analysis.

Because the Doppler waveforms are unaffected by medial arterial calcification, they may be of value in assessing the presence of arterial insufficiency in the diabetic patient. For example, a monophasic waveform at the ankle would be strongly suggestive of proximal arterial disease. However, several limitations exist, especially in the patient presenting with diabetic foot ulceration. Evaluation of the waveform (at the ankle) is qualitative and not quantitative, and therefore the degree of arterial insufficiency is unknown with a monophasic waveform. In addition, in the occasional patient, the waveform may be triphasic at the ankle, but there may be occlusive disease more distally (Fig. 5.7). Furthermore, the quality of the waveforms is technically dependent and affected by multiple variables, including room temperature and the vascular technologist. Finally, extensive casts or bandages preclude accurate waveform measurement.

Pulsed Volume Recordings

The pulsed volume recorder (PVR) is a form of volume plethysmography, which measures the pulsatile volume changes that occur in the limb

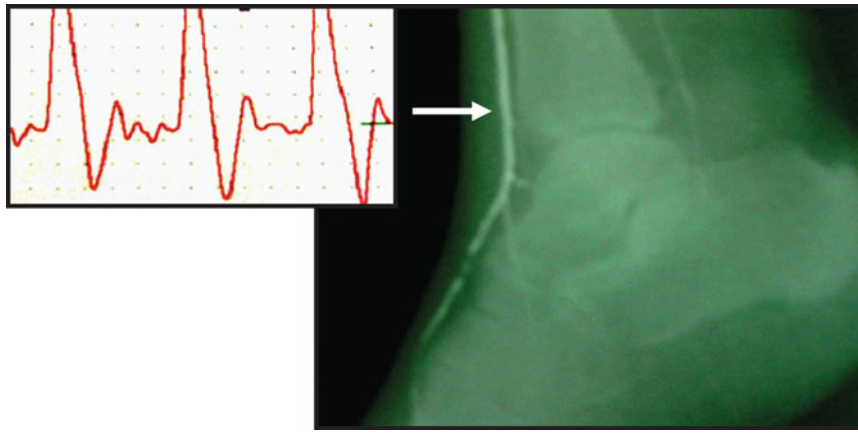

Fig. 5.7 Doppler waveform analysis and arteriogram from the same patient. The Doppler waveform was correctly interpreted as "triphasic at the ankle level"; because of continued nonhealing, arteriogram was performed, demonstrating an occlusive lesion distally

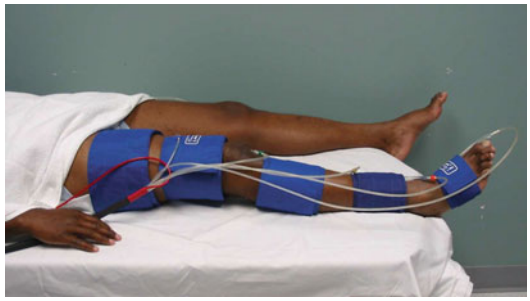

Fig. 5.8 Cuffs placed at various levels for pulsed volume recordings (PVRs)

with each heartbeat. A pneumatic cuff is placed around a specific level of the limb (thigh, calf, and ankle) and inflated with air to a preset pressure between 10 and 65 mmHg (Fig. 5.8). During systole, blood enters the limb, the limb expands, this expansion presses upon the cuff, and the pressure within the cuff increases. During diastole, limb volume is reduced and cuff pressure falls. Therefore, volume changes within a specific level of the limb beneath the cuff are indirectly studied by measuring pulsatile pressure changes within the cuff. These changes are converted into a waveform by a strip recorder.

The normal PVR waveform displays a brisk rise during systole, a sharp systolic peak, a dicrotic notch, and a rapid downslope to baseline (Fig. 5.9a). With mild arterial disease proximal to the level of the tracing, the waveform loses the dicrotic notch and the downslope is more delayed. Increasing severity of proximal occlusive disease results in flattening or rounding of the peak, more delayed systolic upstroke, and reduced amplitude (Fig. 5.9b). In the presence of severe proximal occlusive arterial disease, the PVR waveform will be nearly flatline (consistent with very little volume increase in the limb level during systole) (Fig. 5.9c).

Because the PVR measures volume change and not pressure, it is also unaffected by noncompressible arteries and may be a valuable adjunct in the evaluation of the diabetic foot. However, as with all noninvasive tests, the PVR has several limitations. Although there are some semiquantitative criteria, these have not been correlated clinically, and the test is essentially qualitative. Therefore, a completely normal study is helpful, but it is difficult to quantitate the degree of ischemia with any abnormal study. Indeed, one major shortcoming of the PVR test is that it frequently underestimates the severity of proximal arterial disease (due to the presence of collateral vessels). Additionally, the test is affected by several variables, including room temperature (since temperature differences in the air cuff can change the pressure measured by the air-filled plethysmograph). Peripheral edema and obesity will also affect the quality of the waveforms.

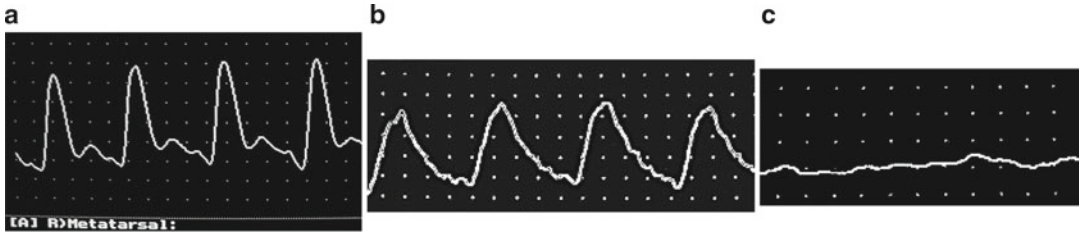

Fig. 5.9 Normal PVR waveform (**a**) with a brisk upstroke, dicrotic notch (*arrow*), and rapid downslope to baseline. (**b**) Evidence of proximal occlusive disease, with loss of the dicrotic notch and a more gradual return of the downslope to baseline. With severe ischemia (**c**), the tracing is flatline

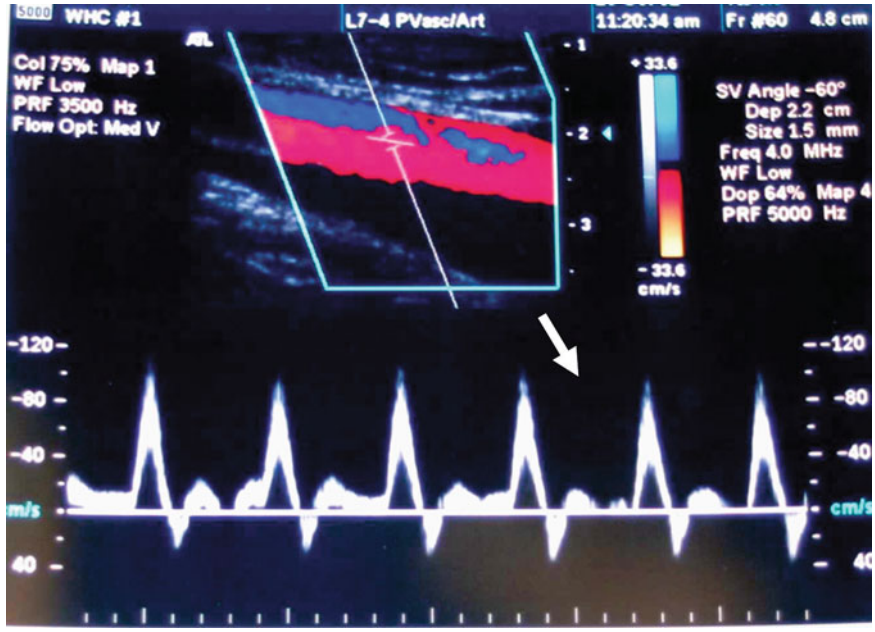

Fig. 5.10 Duplex ultrasound of a normal superficial femoral artery. Note the two modalities of B-mode gray-scale ultrasound (*dashed arrow*) and Doppler-derived tracing (*solid arrow*). The white circle indicates the actual position of the pulsed wave Doppler probe, seen here within the center of the vessel, yielding the Doppler-derived tracing below

Duplex Ultrasound

Duplex scanning employs the dual modalities of B-mode (gray scale) imaging and pulsed wave Doppler spectral frequency analysis. In addition, most Duplex scanners are actually "triplex," with the third modality being color flow imaging. The vessel being insonated may be localized by B-mode imaging, and the pulsed wave Doppler allows for range specificity (Fig. 5.10). Color flow imaging evaluates the Doppler information and determines whether flow is toward or away from the transducer as well as frequency content.

The information obtained from Duplex arterial scanning includes the ultrasound structural characteristics of the artery (wall thickness, type of plaque, etc.), Doppler waveform, velocities, and direction of flow. Analysis of the Doppler waveform characteristics is similar to the preceding discussion on segmental waveform analysis (triphasic, monophasic, etc.), but the principal advantage of Duplex is that the vessel may be

localized by the gray-scale ultrasound (Fig. 5.10). Duplex also allows for an estimation of the degree of stenosis based on velocities and degree of spectral broadening: as an artery narrows, there will be a velocity increase in the stenosis with spectral broadening.

Despite the invaluable role of Duplex ultrasound in the diagnosis of carotid arterial disease and for postoperative graft surveillance, there are multiple limitations in its use for the diagnosis of lower extremity arterial disease. There is a large variation in the range of "normal" velocities for the leg arteries, and therefore a significant stenosis may be misinterpreted. Although the femoral and popliteal vessels may be visualized relatively easily, the tibial vessels are more cumbersome to scan, and the velocities in the tibial arteries may be even more difficult to interpret. When one considers that the usual pattern of vascular disease in diabetes (with a predilection toward atherosclerotic involvement of the tibial vessels), the limitations of Duplex in the diagnosis of arterial insufficiency in the diabetic patient are realized. Because the study depends on accurate sonographic localization of the vessel, Duplex is quite "operator dependent." Finally, multiple other variables can influence the quality of the image, including medial arterial calcification (which can cause artifactual shadowing), obesity, and peripheral edema (which can preclude imaging of the tibial vessels).

Transcutaneous Oxygen Tension ($TcPO_2$) and Laser Doppler Perfusion

Transcutaneous oxygen tension measurements reflect the resting oxygen tension (and the metabolic state) of the underlying tissue. The test involves the placement of a probe (with a sensitized electrode) on the dorsum of the proximal foot, and the local tissue is heated to about 42–44°C. Following an equilibration period, the local resting oxygen tension of the skin is recorded in mmHg. Typically, a value of less than 20 mmHg is associated with critical limb ischemia, and values greater than 60 mmHg are interpreted as normal. Laser Doppler allows for an assessment of skin perfusion. Laser light is transmitted to the tissue via a fiber-optic probe and the returning light is processed. The relative number and velocity of the blood cells in the tissue are calculated as an estimate of perfusion; when a pressure cuff is used, an estimate of the skin perfusion pressure is given, similar to the principles of plethysmography and toe pressures, except that the Laser Doppler probe is used instead of an air plethysmograph.

Because hemodynamics are not measured, these tests are immune to many of the problems facing other noninvasive tests in the presence of diabetes, such as noncompressible vessels. However, due to the unique considerations of the diabetic foot, $TcPO_2$ measurements are not entirely reliable in the diabetic patient with foot ulceration. Although values less than 20 and greater than 60 can be predictive, there is a large "gray area" of intermediate values which are of little clinical use. Additionally, patients with diabetes develop foot ulceration at higher $TcPO_2$ values as compared to the nondiabetic population, and a higher $TcPO_2$ value may not necessarily correlate with healing potential in the diabetic patient (due to the effects of arteriovenous shunting and microvascular dysfunction). Even in the patient with a "normal" $TcPO_2$ value, the measurement may not accurately reflect the healing potential at the target area. Because the probe is typically placed at the proximal dorsal foot (near the ankle), more distal ischemia (due to possible distal tibial and paramalleolar occlusive disease) may not be identified. Technical problems, such as poor probe placement, poor reproducibility, user variability, and lack of familiarity, may also preclude the reliability of the study.

Newer advances in the technology of transcutaneous oximetry have ameliorated some of the problems above. Calibration time has decreased from 20 min to just under 3 min on most machines. Multichannel systems allow for several sites on the leg and foot to be measured simultaneously, allowing for rapid turnover and decreased study time. Laser Doppler-derived skin perfusion pressure has few if any site restrictions, so it allows for an assessment in close proximity to the ulcer. Finally, because these tests are noninvasive and quantitative, they allow for an assessment of the foot following a revascularization procedure,

which may provide helpful prognostic information. However, as with all of the tests listed above, the results should always be used in conjunction with sound clinical evaluation and judgment.

Invasive Arterial Testing: Arteriography

A thorough bedside evaluation in conjunction with selective use of noninvasive vascular testing determines the presence or absence of arterial insufficiency in virtually all patients presenting with diabetic foot ulceration. Once ischemia is judged to be present, revascularization (either as an open surgical procedure or as a percutaneous endovascular intervention) is indicated to maximize the chances of limb salvage. It is at this point that arteriography is appropriate. Because of the inherent risks of any invasive procedure and the risks associated with contrast administration, arteriography is not a diagnostic tool, but rather a part of the therapeutic armamentarium. For this reason, the reader is referred to the management section of this book for a more thorough discussion.

Conclusion

Peripheral arterial disease is common in the patient with diabetes, and is particularly significant in the patient presenting with a diabetic foot problem. A missed diagnosis of arterial insufficiency can lead to protracted wound problems and even limb loss, with associated physical, emotional, financial, and medical–legal calamity. An awareness of the features and strong skills in the diagnosis of peripheral arterial disease help lead to improved outcome and limb salvage.

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Imaging of Infection in the Diabetic Foot

6

Mary G. Hochman

Abstract

Information derived from imaging studies can play an important role in the management of complicated foot problems in the diabetic patient. This chapter reviews the various modalities available for imaging of the diabetic foot—radiography, nuclear medicine studies such as bone scanning, labeled leukocyte scans, gallium, and Flourine-18-flourodeoxyglucose positron emission tomography (FDG PET) scans, cross-sectional studies such as magnetic resonance imaging (MRI), CT, and ultrasound, and various forms of angiography—and highlights their relative strengths and weaknesses for the diagnosis of osteomyelitis, soft tissue infection, and neuroarthropathy. A suggested imaging algorithm for the diagnosis of osteomyelitis in the diabetic foot is presented.

Keywords

Diabetic foot • Osteomyelitis • Neuroarthropathy • Imaging studies • Bone scan • Labeled leukocyte scan • Gallium scan • MRI • CT • US • Angiography

Introduction

Foot infections are among the most common causes of hospitalization in the diabetic population, accounting for 20% of all diabetes related admissions. Complicated foot infections may require treatment by amputation—as many as 6–10% of all diabetic patients will undergo amputation for treatment of infection [1–3], accounting for 57% of nontraumatic lower extremity amputations [4–6]. The scope of the problem is compelling. Infections and complicated vascular diabetic foot problems result in 50,000 amputations a year in the USA [7]. The Centers for Disease Control and Prevention (CDC) estimated the annual treatment cost of amputees within this group at $1.2 billion for the year of 1997. However, this figure does not include the cost of rehabilitation, prosthetic devices, or lost income. These treatment costs are likely to grow, as the prevalence of diabetes is on the rise. A recent

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epidemiology study shows an increase of the overall prevalence of diabetes from 12.1 million in 2002 to 17.5 million in 2007 [8].

Information derived from imaging studies can play an important role in management of complicated foot problems in the diabetic patient. Soft tissue abnormalities such as abscesses and cellulitis can be identified, osteomyelitis can be detected, the extent of abnormal marrow can be depicted, neuroarthropathic changes can be diagnosed and followed over time, distribution of atherosclerotic lesions can be mapped, and the effectiveness of re-vascularizaton procedures can be evaluated. A variety of studies are currently available for imaging the diabetic foot. In order to use these imaging studies effectively, it is important to understand the specific strengths and weaknesses of each modality, as they apply to the particular clinical problem in question. The goal of this chapter is to review the modalities available for imaging of diabetic foot infection and to highlight their relative utilities in the context of clinical problem solving.

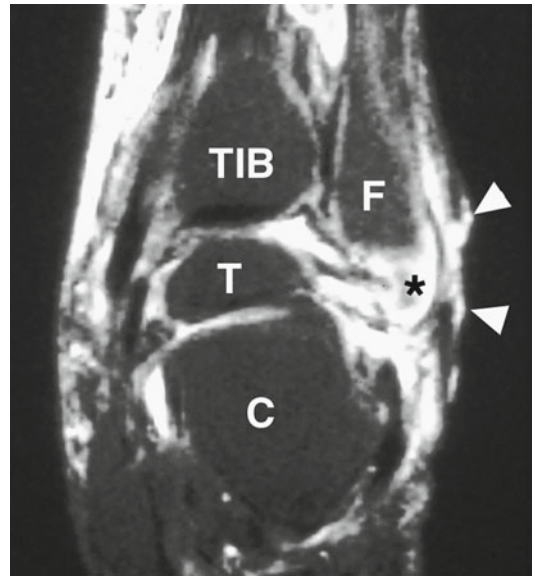

Fig. 6.1 Osteomyelitis deep to ulcer on MRI. Coronal fluid-sensitive STIR image of the left foot of a diabetic patient shows an area of marrow edema (*asterisk*) at the tip of the fibula (F). Overlying this focus of abnormal marrow is an ulcer surrounded by diffuse soft tissue swelling (*arrowheads*). These findings represent osteomyelitis of the distal fibula. *C* calcaneus, *TIB* tibia, *T* talus

Infection in the Diabetic Foot

Risk Factors

Many factors contribute to infection in the diabetic foot, including peripheral neuropathy [9] and vascular insufficiency [10]. Repetitive minor trauma to an insensitive neuropathic foot, exacerbated by abnormal biomechanics or ill-fitting shoes, causes areas of increased plantar pressure to develop callus, which, in turn, predisposes to ulcer development. Clinically occult ulcers form insidiously, deep to the callus [11, 12]. Direct extension of infected ulcers or soft tissue infection to bone leads to osteomyelitis [13] (Fig. 6.1). These infections are usually polymicrobial and involve both anaerobic and aerobic pathogens.

Soft Tissue Abnormalities

Soft tissue abnormalities associated with the diabetic foot include soft tissue edema, cellulitis, soft tissue abscess, ulcers, sinus tracts, tenosynovitis, joint effusions, and arthritis [14–16]. The importance of differentiating these conditions lies in their differing management: abscess necessitates prompt surgical drainage, septic arthritis requires surgical debridement, and cellulitis generally entails antibiotic therapy.

Soft tissue edema and swelling is a common finding in the diabetic patient. Soft tissue swelling can occur in the absence of infection, due to vascular insufficiency or peripheral neuropathy (Fig. 6.2) [16]. However, soft tissue swelling can also reflect the presence of cellulitis, that is, soft tissue infection of the superficial soft tissues. Cellulitis along the dorsum of the foot usually occurs secondary to surface infections in the nails, toes, or Web spaces. Simple cellulitis is generally diagnosed clinically, without the need for imaging. The major indication for imaging of patients with cellulitis is suspected underlying deep infection, such as soft tissue abscess, osteomyelitis, or septic arthritis.

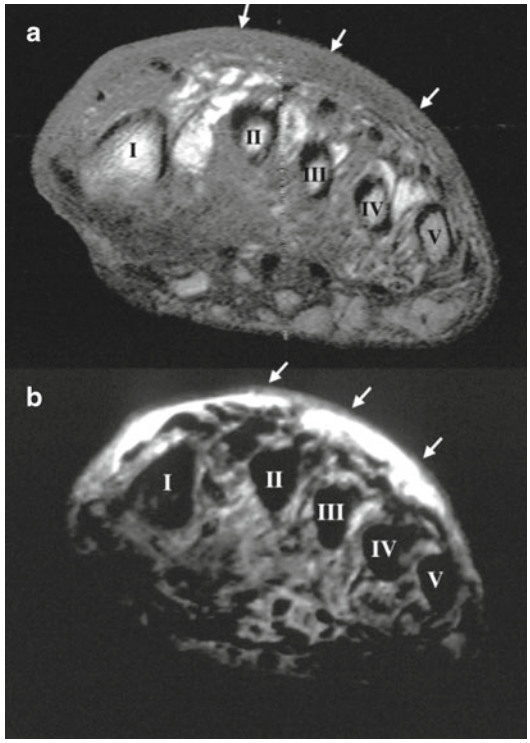

Fig. 6.2 Dorsal soft tissue swelling on MRI. (**a**) T1-weighted image and (**b**) fluid-sensitive STIR image are coronal or short axis images acquired at the level of the mid-metatarsal shafts. This diabetic patient has diffuse dorsal soft tissue swelling (*small arrows*). The subcutaneous edema is dark or low signal on the T1-weighted image and bright or high signal on STIR. Note the presence of normal fatty marrow signal in the metatarsal bones—high signal (*bright*) on T1 and low signal (*dark*) on STIR, conclusively ruling out osteomyelitis. *I–V* first to fifth metatarsals

Osteomyelitis

Osteomyelitis of the foot occurs up to 15% of diabetic patients [15]. Bone infection results from local extension of soft tissue infection (Fig. 6.1). Callus and ulcers serve as the conduits for infection to spread to deep soft tissue compartments, bones, and joints. The most common sites of soft tissue infection and secondary osteomyelitis are foci of increased plantar pressure, such as the metatarsal heads and the calcaneus (Fig. 6.3). Evaluation of foot ulcers is important because more than 90% of osteomyelitis cases result from contiguous spread of infection from soft tissue to bone [7]. Newman et al. further demonstrates a clear relationship between ulcer depth and osteomyelitis: 100% of ulcers exposing bone and 82% of moderately deep ulcers were shown to have osteomyelitis on bone biopsy [1] (Fig. 6.1).

Identification of osteomyelitis in the diabetic foot can be difficult both clinically and radiographically. Ability to probe a pedal ulcer through to bone (Fig. 6.3) has been reported as a useful index of underlying osteomyelitis in a diabetic patient [17] and is commonly used to guide decisions regarding treatment. Nonetheless, clinical judgment was shown to be a poor indicator of infection. The technique of probing to bone, only 68% sensitive, may underestimate the incidence of bone involvement, according to Newman et al. [1]. In the same study, 18 out of 19 of pedal ulcers did not expose bone nor display inflammation, yet contained osteomyelitis. Moreover, other clinical parameters such as fever and leukocytosis are unreliable in the diabetic patient. For example, in a study by Bamberger et al., only 18% of patients with clinically severe osteomyelitis were febrile [13]. Neither fever nor leukocytosis predicts the necessity for surgical exploration [18].

Imaging Modalities

Imaging can play a role in diagnosing and distinguishing between bone and soft tissue infection, characterizing soft tissue abnormalities, identifying osteoarthopathy and other bony abnormalities, and mapping vascular disease for surgical intervention. A variety of imaging modalities can be useful in the evaluation of the diabetic foot, include radiography, scintigraphic examination, CT, magnetic resonance imaging (MRI), US, and angiography. Imaging techniques vary in their sensitivity for detection of osteomyelitis, with specificity limited in the presence of cellulitis, peripheral ischemia, and diabetic neuropathic osteoarthropathy [19, 20] (Table 6.1). In the appropriate setting, however, noninvasive imaging can aid in diagnosis and treatment planning.

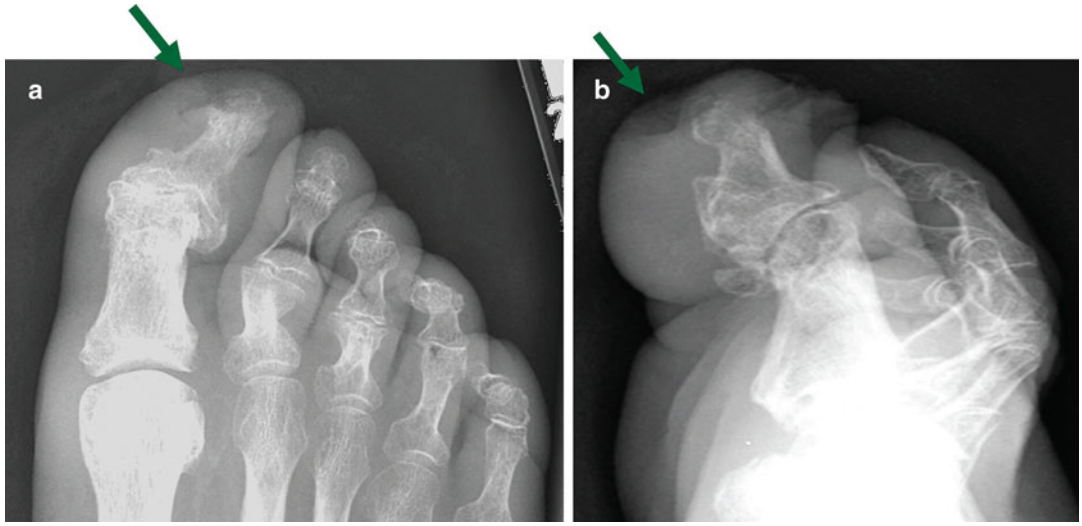

Fig. 6.3 Osteomyelitis of first distal phalanx. (**a**) AP and (**b**) lateral views of the great toe show an ulcer (*arrow*) overlying the distal phalanx. The cortex of the bone is indistinct and there is underlying osteopenia, representing osteomyelitis. On clinical examination, exposed bone was evident at the ulcer

Table 6.1 Compilation of sensitivity and specificity of various imaging modalities in the diagnosis of osteomyelitis

	Range of sensitivity (%)	Range of specificity (%)	Compiled sensitivity/specificity (%/%)	References
Radiography	52–93	33–92	61/72	[26, 27, 31, 80, 82, 83, 102, 126–128]
Three-phase bone scan in patients without bone complications			94/95	[23] Review of 20 published reports
Three-phase bone scan in patients with bone complications			95/33	[23]
In-111 labeled WBC	75–100	69–100	93/80	[26, 27, 31, 129]
Combined gallium and bone scan			81/69	[23]
MRI	29–100	67–95	96/87	[80–84, 129]

Radiographs

Radiography ("X-ray") remains the first screening examination in any patient with suspected infection and have the advantage of being inexpensive and easily obtainable. Radiographs can help to identify an unsuspected diabetic patient by demonstrating calcification in the interdigital arteries: these vessels rarely calcify in nondiabetic patient [21]. Cellulitis results in increased density and thickening of the subcutaneous fat, though nonspecific soft tissue edema can have a similar appearance. Both bone and soft tissue infection can result in blurring of usually visible fat planes. Focal fluid and callus both demonstrate focal increased density in the subcutaneous fat. Ulcers may or may not be visible on radiographs, depending on their size and orientation. (Fig. 6.5). In general, all of these soft tissue abnormalities are more clearly evident at physical examination. However, radiographs do readily depict subcutaneous emphysema associated with infection or recent surgery (Fig. 6.4). Some foreign bodies, i.e., denser materials such as

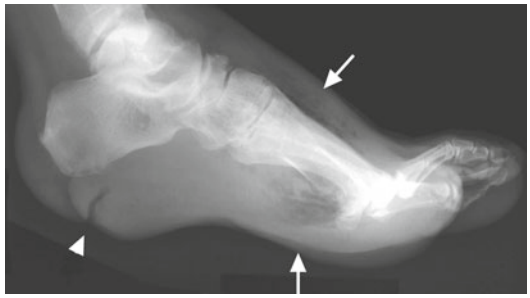

Fig. 6.4 Soft tissue air and deep ulcers on radiography. The lateral view of the right foot from a diabetic patient shows subcutaneous air (*arrows*) in both dorsal and plantar soft tissues surrounding the metatarsals. A deep ulcer dissects into the heel fat pad (*arrowhead*)

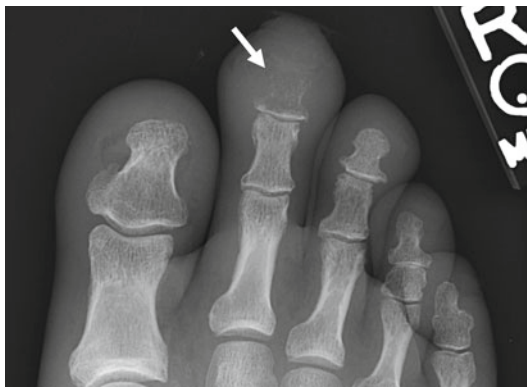

Fig. 6.5 Osteomyelitis of the second distal phalanx. Extensive destruction of cortical and medullary bone (*arrow*), with surrounding soft tissue swelling

metal and lead-containing glass are radio-opaque and generally are visible on radiographs. In order to detect nonmetallic foreign bodies and subtle soft tissue calcifications, radiographs acquired with "soft tissue" technique (i.e., lower kV than a routine radiograph) may be required.

Findings of osteomyelitis on radiographs include soft tissue swelling and effacement of tissue fat planes, permeative medullary radiolucency, focal osteopenia or focal osteolytic lesion, periosteal new bone formation, endosteal scalloping, and cortical bone destruction (Table 6.2; Figs. 6.3–6.5). Of note, these osseous changes typically only become apparent after osteomyelitis has been present for 10–14 days and require up to 50% bone loss before becoming evident on a radiograph [22]. Comparison to prior films, when available, can help to highlight early changes. In the majority of studies, sensitivity of radiographs ranges between 52 and 93% and specificity ranges between 33 and 92%, for detection of osteomyelitis (Table 6.1). When radiographs are positive for osteomyelitis, further imaging studies are often not required. However, radiography is less sensitive compared with other imaging modalities and a negative X-ray examination does not exclude osteomyelitis. Moreover, radiographs are not sensitive for detection of soft tissue infection, such as septic arthritis or abscess formation.

Table 6.2 Radiographic findings of acute osteomyelitis

Soft tissue swelling and effacement of soft tissue fat planes
Permeative medullary radiolucency
Focal osteopenia or focal osteolytic lesion
Periosteal new bone formation
Endosteal scalloping
Cortical bone destruction

Even when radiographs do not demonstrate findings of osteomyelitis, they nonetheless play an important role in the diagnostic-work-up of infection. Because they demonstrate changes of neuroarthropathy, postsurgical changes, fractures, foreign bodies, gas, foot deformities, and bony variants, radiographs can serve as roadmaps for other imaging examinations. In the absence of correlative radiographs, these findings can cause unnecessary confusion on MRI or nuclear medicine examinations.

Nuclear Medicine

The three most commonly employed nuclear medicine or scintigraphic tests for the diagnosis of diabetic foot infection are bone, labeled leukocyte scans, and gallium scans. FDG PET has shown utility for diagnosing musculoskeletal infection, but is not yet routinely reimbursed for this indication. Bone, labeled leukocyte, and gallium scans are all considered highly sensitive to the presence of both soft tissue infection and

osteomyelitis (Table 6.1). When the foot is radiographically normal, bone scan is the scintigraphic examination of choice. When preexisting bone changes are present (i.e., neuroarthropathy, trauma, degenerative changes), labeled leukocyte scan provides the best overall sensitivity and specificity among the nuclear medicine studies (Table 6.1).

Bone Scan

Traditionally, triple phase bone scan (TPBS) has been the test used for the work-up of suspected osteomyelitis in patients with negative radiographs. It is widely available and easy to perform. A three-phase bone scan involves intravenous injection of radioactive technetium-99m methylene diphosphonate, followed by imaging with a gamma camera at three distinct time points. Images acquired every 2–5 s immediately following injection provide a radionuclide angiogram (the flow phase) and may demonstrate asymmetrically increased blood flow to the region of interest. The tissue or blood pool phase is obtained within 10 min and reveals increased extracellular fluid seen in conjunction with soft tissue inflammation. A delayed, skeletal phase is acquired 2–4 h after the injection. The skeletal phase demonstrates areas of active bone turnover, which have incorporated the radionuclide tracer, and are seen as focal "hot spots" of increased tracer activity. The tracer is taken up by bone in an amount dependent on both the degree of osteoblastic activity and the blood flow to the area. In some facilities, single-photon emission computer tomography (SPECT) spanning can be performed in conjunction with a technetium bone scan to generate tomographic, cross-sectional images of radionuclide activity that can be reformatted into different planes and can help to clarify problems created by bony overlap. Because SPECT images have greater intrinsic contrast than routine planar images, the SPECT images are also more sensitive in detecting foci of radionuclide activity.

Osteomyelitis results in increased uptake in all three phases of a bone scan, whereas simple cellulitis demonstrates increased uptake in the first two phases only (flow and tissue or blood pool phases) (Fig. 6.6). In cellulitis, there may be mild diffuse increased uptake in the bone due to inflammation, but this is distinct from the more focal, intense increased uptake seen with osteomyelitis. However, uptake in the delayed phase itself is not specific for osteomyelitis. In general, a positive delayed phase scan is seen when there is an underlying process that promotes bone remodeling, e.g., healing fracture, neuropathic osteoarthropathy, or recent bone surgery. False negatives may occur when the radiotracer fails to reach the foot because of diminished vascular flow. This is of particular concern in diabetics with atherosclerotic disease.

Schauwecker's review of 20 published reports shows a compiled mean sensitivity and specificity of 94% and 95%, respectively, for detection of osteomyelitis with bone scintigraphy [23]. Unfortunately, this data applies only to patients without underlying bone deformities. In the diabetic patient with complicated bone conditions such as recent fractures and neuroarthropathic changes, a common clinical presentation, the sensitivity remains at 95%, but the specificity declines to 33% [23]. Thus, the American College of Radiology (ACR)-sponsored appropriateness criteria for detection of osteomyelitis recommends a three-phase bone scan only when radiographic findings of bone complications are absent [24]. If radiographic findings of bone complications are absent and the bone scan is normal, then there is little likelihood of osteomyelitis and the investigation can be considered complete. However, when the radiograph reveals an underlying focal bony abnormality, then a bone scan is unlikely to be definitive and, therefore, a labeled leukocyte study or MRI is recommended instead. If a labeled leukocyte scan or MRI is not available, a gallium scan may provide a useful alternative.

Labeled Leukocyte Scan

Labeled leukocyte scans, also known as labeled white blood cell (WBC) scans, are the preferred scintigraphic technique for imaging when there is background bone pathology on radiographs. This is because WBCs accumulate at sites of infection, but, unlike bone scans, they do not accumulate at sites of increased bone turnover, such as

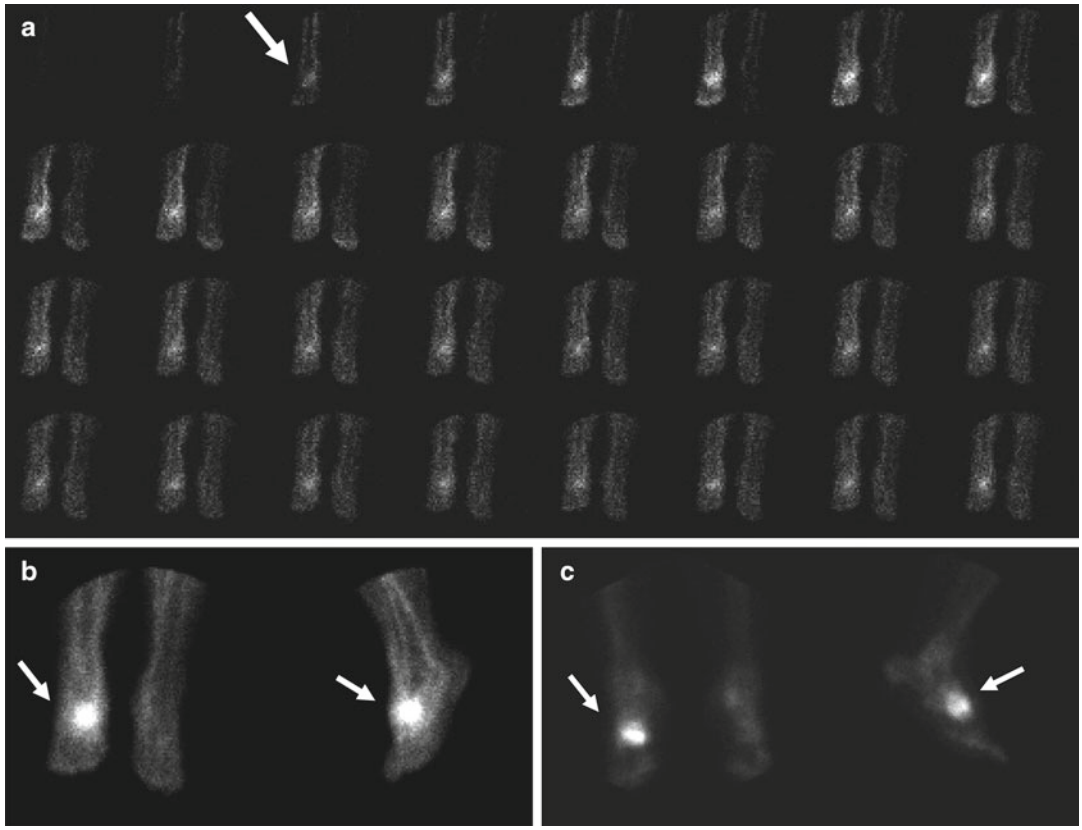

Fig. 6.6 Osteomyelitis on triple phase bone scan (TPBS). (**a**) Radionuclide angiogram (flow phase) of a TPBS with successive images obtained every 2–5 s following injection, showing asymmetrically increased blood flow to the distal right lower extremity (*arrow*). (**b**) Blood pool phase obtained within 10 min after injection shows increased activity in the right foot (*arrows*), reflecting increased extracellular fluid related to soft tissue inflammation. AP view on the left and lateral view on the right. (**c**) Delayed skeletal phase acquired 2–4 h after injection shows increased activity in the bones of the midfoot. In this phase, "hot spots" reflect areas of active bone turnover (*arrows*) and is therefore specific for bone. Note that the signal seen in the soft tissues on the preceding blood pool phase has cleared. AP view on the *left* and lateral view on the *right*

fractures and neuropathic osteoarthropathy. WBC scans are performed by extracting a patient's blood, fractionating the leukocytes from blood, incubating the WBCs with either indium 111-oxine or technetium-99m-hexamethylpropylene amine oxime (Tc-HMPAO) in order to label them, and then re-injecting the labeled WBCs into the same patient. Imaging is performed 16–24 h later, using a standard gamma camera. As noted above, labeled WBCs theoretically only accumulate at sites of infection and not at sites of increased osteoblastic activity and therefore should be extremely useful in the diagnosis of complicated osteomyelitis (Fig. 6.7). The technique is most useful for inflammatory processes that are mediated by neutrophils, such as bacterial infections, since the majority of leukocytes labeled are neutrophils [25]. In addition, a total white count of at least 2,000/μL is needed to obtain satisfactory results [25].

Indium-labeled leukocyte scan offers the best sensitivity and specificity among the three readily available scintigraphic techniques (Table 6.1). A compilation of seven studies yielded a sensitivity of 93% and specificity of 80% [1, 26–31]. In addition, Newman suggested that indium-labeled leukocyte imaging could be used to monitor response to therapy, with images

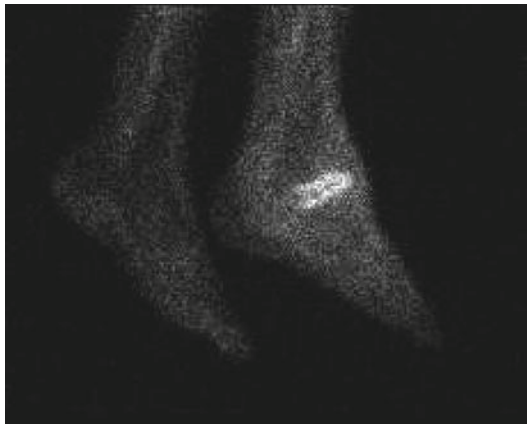

Fig. 6.7 Osteomyelitis on indium-labeled leukocyte scan. Increased indium accumulation about the ankle represents a focus of osteomyelitis in a patient with swelling and fever. Staph aureus grew from the marrow aspirate

reverting to normal 2–8 weeks after commencement of antibiotic therapy [1].

Despite their potential advantages and reported high sensitivity and specificity, indium-labeled leukocyte scans have not completely displaced other imaging modalities. Recent data shows false-positive uptake of indium-labeled leukocytes in as many as 31% of noninfected neuropathic joints [32]. These false-positive examinations stem from the inability to determine whether labeled leukocytes located outside the typical marrow distribution represents infection or merely an atypical site of hematopoietic activity [33]. Atypical patterns of marrow distribution may accompany fractures, orthopedic hardware, infarctions, systemic diseases, and tumors. At sites where bone marrow may be present, it is very helpful to compare the leukocyte scan with a bone marrow scan obtained with technetium-99m-macroaggregated albumin. False-negative examinations may occur when the procedure for labeling the leukocytes is inadequate [34]. Detection of osteomyelitis is rarely a problem in the forefoot, where the osseous structures are equidistant from both dorsal and plantar skin surfaces, but may be compromised in the mid- and hindfoot due to anatomic complexity in these areas [33]. Interpreting the labeled leukocyte study in conjunction with the anatomic localizing information available from a simultaneously acquired bone scan can help to improve accuracy [31].

Technitium-99m HMPAO-labeled leukocyte scans are reported to be as accurate as indium-labeled leukocyte studies in the diagnosis of osteomyelitis. This technique of labeling has the advantage of providing the results on the same day and depositing a much lower radiation dose. Its major drawback is that it does not permit simultaneous acquisition with bone or bone marrow scans.

Other disadvantages associated with both indium- and technetium-99m HMPAO-labeled leukocyte scans include the complexity of the labeling process, high costs, limited availability of the test, and the risks inherent in handling of blood products. Because of the difficulties inherent in in vitro labeling of leukocytes, several techniques for in vivo labeled leukocyte imaging have been developed. However, these techniques are not at present in widespread use [25].

Gallium Scan

Gallium is not frequently used in work-up of diabetic pedal osteomyelitis, but can be a useful alternative for assessment of pedal infection when there are abnormal radiographic findings on a foot radiograph and a labeled leukocyte scan or MRI is not available. Gallium-67 citrate localizes in areas of infection. If the gallium scan is normal, osteomyelitis can be excluded. By itself, gallium is not very specific for the diagnosis of osteomyelitis, because gallium accumulates not only at sites of bone infection but also at sites of soft tissue infection and at sites of increased bone remodeling, as seen in trauma [35]. Gallium scan images frequently lack spatial resolution, which precludes separation of bone from soft tissue uptake [35] (Fig. 6.8). If there is any bony abnormality, then a bone scan should be obtained prior to obtaining the gallium scan, in order to improve the specificity of diagnosis. (The long half-life of gallium-67 makes it prudent to acquire the bone scan first.) In that case, if the gallium scan is positive, then the uptake on the bone scan can be used to account for the gallium uptake that is occurring due to bony remodeling [36]. The diagnosis of osteomyelitis is made when the gallium and

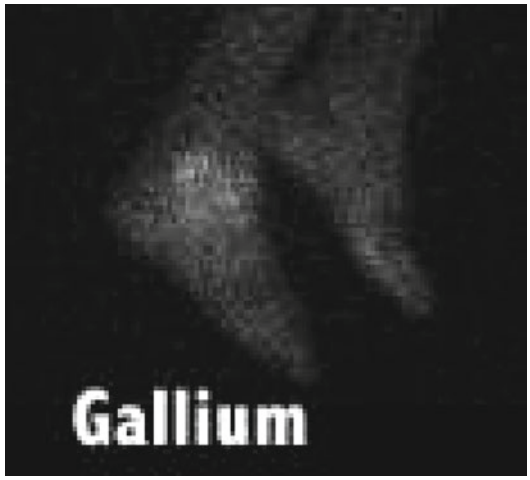

Fig. 6.8 Osteomyelitis of left ankle on gallium scan. The increased gallium activity in the distal tibia of a diabetic patient suggests osteomyelitis. However, the lack of resolution of the image precludes distinction of bone versus soft tissue inflammation

Table 6.3 Criteria for diagnosis of osteomyelitis using combined bone and gallium examinations [35]

Gallium uptake exceeds bone scan uptake
Gallium and bone scan uptake are spatially incongruent

bone scan are incongruent, as summarized in Table 6.3.

Schauwecker showed the sensitivity and specificity of this technique to be 81% and 69%, respectively [23]. However, the author also observed that more than half of the combined bone and gallium examinations were equivocal. This technique, therefore, is only helpful when the study is positive or negative. Although the relatively high number of equivocal examinations makes this modality less advantageous, gallium scan remains a useful alternative if labeled leukocyte scan or MRI is not available.

FDG PET Scan

Flourine-18 labeled fluorodeoxyglucose (FDG) imaging using positron emission tomography (PET) has become an important technique for oncologic imaging and is in common clinical use for detection, staging, and monitoring response to therapy in lung cancer, breast cancer, lymphoma, and melanoma, among others [37]. However, FDG PET scans often also show increased activity in areas of inflammation or infection and the use of PET for these nonneoplastic applications is now being actively investigated [37]. At this early juncture, however, FDG PET examinations are not routinely reimbursed for applications related to infection.

FDG is a radiolabeled glucose analogue that is taken up by cells in proportion to their metabolic rate and number of glucose transporter proteins. Increased FDG uptake is seen in inflammation, due to increased expression of glucose transporters and increased affinity for the glucose analogue by activated inflammatory cells. The fluorine-18 (^{18}F) radionuclide is produced in a particle accelerator known as a cyclotron and has a relatively short radioactive half-life. After intravenous injection of flourine-18 FDG, a patient is imaged 30–60 min later using a PET scanner. A routine examination includes images from the level of the skull base through the mid-thigh, though examinations spanning the skull to the feet can be performed. Areas of increased activity on the images reflect sites of increased glucose metabolism and may be described in terms of standardized uptake value (SUV). Many of the scanners currently being installed are PET-CT scanners, which incorporate both a PET scanner and a conventional CT scanner, In a PET-CT system, PET and conventional CT images are both obtained during the same examination and can be fused together into hybrid images, to aid in localization of areas of increased activity. This improved localization capability can be used, for example, to help distinguish between osteomyelitis and soft tissue infection [38].

FDG PET has shown promising initial results for imaging of infection, but remains an investigational technique. In general, sensitivity for infection tends to be relatively high and negative predictive value is very high, but false positives can occur because any area of increased metabolic activity—not just infection—will show increased radionuclide activity. Recent surgery can also result in false-positive increased activity [37]. Chacko et al. examined 167 PET scans in 175 anatomic sites and found an accuracy of

91.2% for chronic osteomyelitis [39]. Meller et al. prospectively compared FDG PET and labeled leucocytes and concluded that FDG was superior for the diagnosis of chronic osteomyelitis [40]. PET has also shown utility in evaluation of chronic osteomyelitis and infected prostheses [41]. In a meta-analysis by Termaat et al., FDG PET shows a pooled sensitivity of 96% and a specificity of 91% for the diagnosis of chronic osteomyelitis [42]. In a limited number of cases, correlative decreases in FDG uptake and inflammatory activity have been reported following antibiotic treatment [43], suggesting a potential role in tracking response to therapy, analogous to its current use in tumor treatment [37, 44]. A series of novel PET tracers are currently being evaluated for imaging of infection and inflammation [41]. Overall, FDG PET has shown good sensitivity for imaging of osteomyelitis [45], but is not yet reimbursed for this indication.

Specific data on the use of FDG PET for assessment of infection in the diabetic foot remains limited. Keider et al. examined 18 sites of infection in 14 patients and demonstrated that FDG PET could help to precisely localize infection and could distinguish between bone and soft tissue infection in the diabetic foot [38]. By contrast, in a study by Schwegler et al. that included seven diabetic patients with chronic foot ulcers and biopsy-proven osteomyelitis, FDG was positive in only two cases, while MRI was positive in six [46].

Compared with WBC scans, FDG PET offers shorter examination times and obviates the need for drawing WBCs from the patient for labeling. PET is less susceptible than WBC scans to false negatives resulting from decreased perfusion at the infection site. While PET and WBC scans are thought to be comparable in sensitivity in the peripheral skeleton (where there is usually a paucity of hematopoietic marrow to cause spurious WBC activity), PET is considered more effective than WBC scans for detection of central foci of infection/inflammation, because of physiologic uptake of WBCs by bone marrow in the axial skeleton [37]. A potential concern related to the use of PET in diabetic patients relates to the effect of chronic hyperglycemia on FDG uptake in metabolically active lesions [47].

Newer Radiopharmaceuticals

A number of new radiopharmaceuticals that may have application in the diagnosis of diabetic foot infection are being investigated, but have not entered routine clinical practice. These include radiolabeled antigranulocyte antibodies, immunoglobulins, and antibiotics.

Computed Tomography

Computed Tomography (CT) scans can show findings of osteomyelitis earlier than radiographs, but are not considered a front-line examination for the diagnosis of osteomyelitis, because they are less sensitive than MRI for soft tissue and osseous infection and also because, unlike MRI, they expose the patient to ionizing radiation.

CT scans use ionizing radiation to generate cross-sectional scans of the body. Tissues are displayed on a gray scale that reflects their relative X-ray attenuation, a quantity that is expressed in Hounsfield units (HU). For example, Hounsfield units typically measure −1,000 for air, 0 for water, ~ 40 for soft tissue, and ≥400 for bone. Most CT scans are now performed on multidetector scanners, which allow acquisition of thinner cross-sectional images and faster imaging times. When thin-section "volumetric" scans are acquired with a multidetector scanner, image sets acquired in one plane can be reformatted computationally into any desired imaging plane, after they have been acquired, e.g., images acquired axially can be reformatted into coronal or sagittal images. Image data can be postprocessed with different algorithms to highlight either bones or soft tissues. Independent of that postprocessing, images can also be displayed using "bone" or "soft" tissue windows. Image data can also be postprocessed to highlight anatomy in different ways, such as maximum intensity projection (MIP images) to produce a CT angiogram or volume rendering (VR) to create a 3D display of various tissues.

CT scans are often performed using intravenous iodinated contrast, in order to highlight different tissues, demonstrate characteristic enhancement patterns of certain structures,

outline cysts and fluid collections and distinguish them from solid masses, and depict vascular anatomy. In most cases, CT contrast administration is uneventful. However, some patients experience reactions after IV administration of iodinated contrast, with fatal anaphylactoid reactions in approximately 1 in 40,000 patients [48]. The risk of reaction is significantly reduced with low osmolar nonionic contrast, now in routine use at many institutions [49]. Use of nonioinic contrast also decreases the incidence of nausea, vomiting, hemodynamic instability, and discomfort or pain associated with contrast administration, effects that are relate to the osmolality of the contrast [49, 50]. In patients with a history of contrast allergy, nonionic contrast, together with oral methylprednisolone as a premedication, can be used prior to contrast administration. Patients with elevated creatinine (>1.5 mg/dL) and diabetes (especially insulin dependent diabetes) are at increased risk for contrast-induced renal failure due to acute tubular necrosis [51]. Contrast-induced nephropathy occurs with both ionic and nonionic contrast, although less frequently with nonionic forms. The overall incidence of contrast-induced renal failure is low (1–2% in patients with normal renal function) [49] and the effect is usually brief and self-limited. However, the rate is significantly higher in patients with renal failure (10% in patients with serum creatinine 1.3–1.9 mg/dL and up to 65% with levels >2 mg/dL) [49]. Moreover, contrast-induced renal insufficiency in a patient on the oral hyperglycemic agent dimethylbiguanide (Metformin) can result in fatal lactic acidosis, leading to the recommendation that Metformin should be withheld prior to and following contrast administration [49]. Intravenous hydration is used as a preventive measure in this setting; the use of diuretics may be deleterious [52].

Advantages of CT include high spatial resolution of CT images, superb depiction of bony detail and small calcifications, and the ability to image large areas of anatomy in a single, rapid scan. Disadvantages of CT include exposure to ionizing radiation and risks associated with contrast administration. Of note, the radiation dose from scanning extremities is significantly less than that associated with scans through the torso. Orthopedic hardware can cause "beam hardening" artifact that obscures surrounding anatomy, but, with newer generations of scanners, the effects are less pronounced than they have been in the past. Nonetheless, stents, dense prostheses, and large metallic constructs can pose problems for diagnostic imaging.

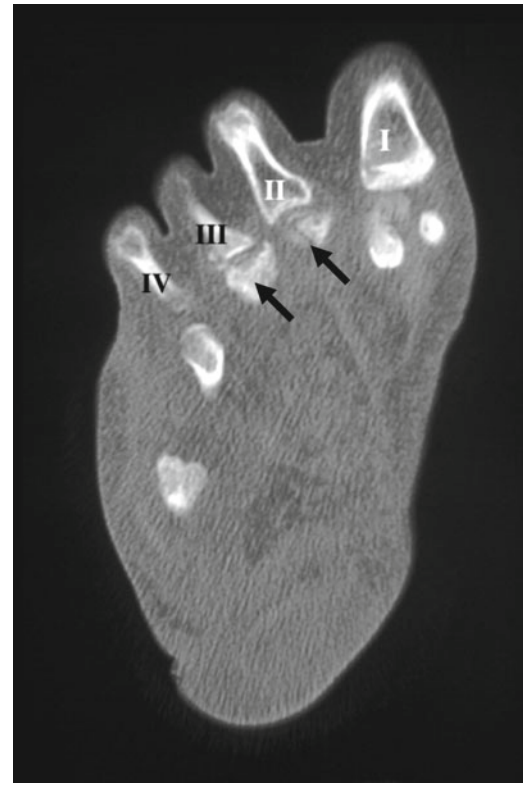

Fig. 6.9 Metatarsal osteonecrosis on CT. The second and third metatarsal heads are flattened. The radiolucencies beneath the deformed metatarsal heads represent subchondral fractures (*arrows*). CT exquisitely demonstrates these cortical abnormalities

During early stages of acute osteomyelitis, changes may be difficult to detect on radiography, but can frequently be documented on CT. CT is superior to radiography in detection of cortical destruction (Fig. 6.9), periostitis, and soft tissue or intraosseous gas [53, 54]. CT can also demonstrate increased density of intraosseous medullary fat and blurring of soft tissue fat planes due to the presence of pus and edema [55, 56]. CT is extremely effective in demonstrating a

bony sequestrum when present in chronic osteomyelitis (a focus of necrotic bone insulated from viable bone by granulation tissue). The sequestrum appears as a dense bone spicule situated within the medullary cavity and surrounded by soft tissue density [7, 57]. CT scan is useful for detection of radiographically occult foreign bodies, even those that are not traditionally considered radio-opaque (e.g., wood). While CT scans performed with intravenous iodinated contrast material can demonstrate soft tissues abscesses and necrotic tissue as areas of nonenhancement imaging modalities that possess superior intrinsic soft tissue contrast resolution, MRI and ultrasound are better suited to imaging of abscess collections and, when necessary, can be performed in the absence of intravenous contrast. Thus, use of CT for detection of soft tissue abscess should be weighed against the risk of contrast-induced complications. Overall, the data on sensitivity or specificity of CT for diagnosis of diabetic pedal osteomyelitis is scant. In light of concerns regarding risks of ionizing radiation, allergic reaction to contrast, and, in particular, contrast-induced nephropathy, there appears to be little enthusiasm for using CT as a routine diagnostic test for osteomyelitis.

Ultrasound

Gray-scale ultrasound has very limited application in imaging of bone and bone infection, because of the acoustic shadowing caused by cortical bone, though ultrasound has been used to image soft tissue infection and subperiosteal abscesses and can be used to guide aspiration of soft tissue infection. (Duplex Doppler ultrasound imaging of vasculature in the diabetic foot is discussed separately below.)

Ultrasound images are produced using an ultrasound transducer to transmit and receive ultrasonic waves of given frequencies, by holding the transducer against a patient's skin [58]. The amplitude of the sound that is reflected back (rather than transmitted forward) is translated into a gray-scale image of the underlying anatomy. Areas of interest are described based on their resultant echogenicity. Areas that transmit ultrasound waves with negligible reflectance, such as simple fluid, appear uniformly dark and are termed anechoic; areas that are highly reflective of sound waves, such as cortical bone, appear bright and are termed hyperechoic. Different tissues, such as muscles, tendons, and nerves, when normal, have characteristic reflectance patterns. Diagnostic ultrasonography of the foot is performed using a high-frequency transducer, often in conjunction with a stand-off pad.

Ultrasound has many advantages for imaging the diabetic patient. Ultrasound examinations do not involve ionizing radiation, entail minimal patient discomfort, and can often be performed in small children without the use of sedation. Ultrasound can be performed in patients who might have contraindications to MRI and can often yield diagnostic examination in cases where orthopedic hardware might preclude successful imaging by MRI or CT. Ultrasound equipment is relatively low cost, easily transportable, and is more widely available than MRI in many countries. Unlike many other imaging modalities, ultrasound readily provides real-time imaging and therefore can be used to assess motion and to guide aspirations, biopsies, and therapeutic injections. The major—and important—disadvantage of ultrasound is that it requires a high level of operator and interpreter expertise.

Ultrasound is well-suited for evaluation of superficial soft tissues and for guiding aspiration and drainage of intra- or extra-articular fluid collections. Abscesses are seen as hypoechoic collections with increased through transmission (i.e., the tissue deep to the abscess appears more echogenic than expected, because the sound waves are attenuated to a lesser degree by the fluid in the abscess than by the soft tissue surrounding the abscess) (Fig. 6.10). However, an abscess may be difficult to identify on ultrasound when its contents become proteinaceous, because it can then become isoechoic to the surrounding tissues and may fail to demonstrate enhanced signal in the tissues deep to the abscess. Similarly, joint effusions are often visible as hypoechoic on ultrasound, but may be less evident when their contents are complex. Even when sonography

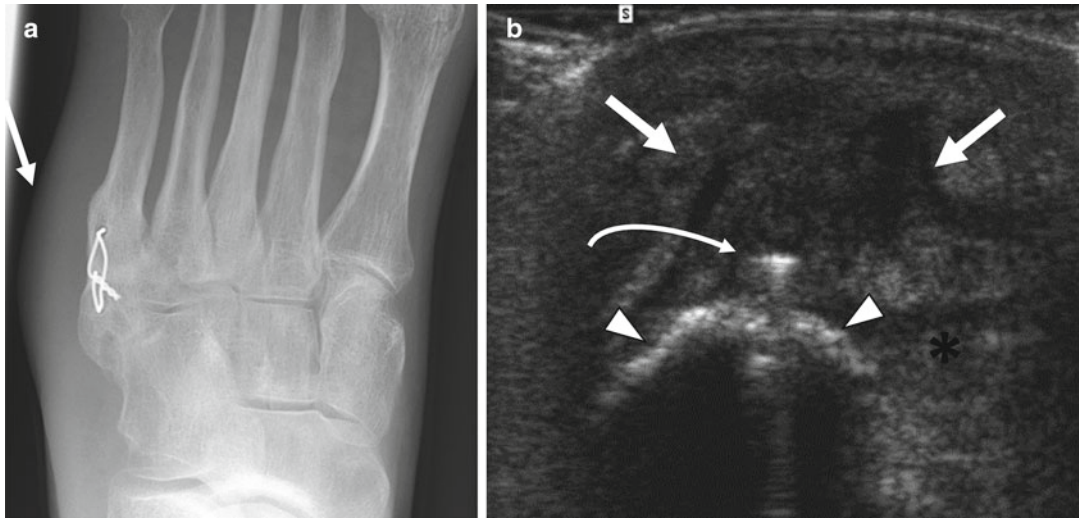

Fig. 6.10 Soft tissue abscess on ultrasound. (**a**) AP radiograph of the foot shows soft tissue swelling adjacent to the fifth metatarsal (*arrow*), but does not distinguish between generalized soft tissue swelling and detection of a focal abscess. (**b**) Gray-scale ultrasound image obtained in cross-section to the base of the fifth metatarsal shows a complex fluid collection in the overlying soft tissues (*arrows*), consistent with an abscess. Simple fluid appears anechoic (*dark*), but more complex components are similar in echogenicity to—and harder to distinguish from—surrounding tissues. The bright, hyperechoic curvilinear line is the cortex of the bone (*arrowheads*). The dark, anechoic area below the cortex is caused by acoustic shadowing from the cortex and (routinely) precludes ultrasound evaluation of the medullary cavity. The small bright area immediately above the cortex (*curved arrow*) represents an orthopedic wire. The bright, hyperechoic area next to the bone (*asterisk*) represents enhanced-through transmission, a sign that the tissue above it has fluid content

demonstrates a fluid collection, the presence or absence of infection within the fluid cannot be established by imaging. Thus, ultrasound is often employed for guiding aspiration of the suspect fluid collection.

Ultrasound is not very useful for direct evaluation of osteomyelitis, particularly early osteomyelitis, because cortical bone causes acoustic shadowing that obscures the underlying bone [59] (Fig. 6.10). In children, the use of ultrasound to demonstrate subperiosteal abscesses has been described [60, 61]. Subperiosteal abscess is a feature of osteomyelitis in children, but not adults, because, in children, the periosteum is more loosely adherent to the bone and, therefore, more easily displaced by pus. Subperiosteal abscess appears as an anechoic or moderately echoic zone >2 mm thick, adjacent to the bone and can be detected prior to changes on plain radiographs [62, 63]. Care must be taken not to mistake soft tissue abscess or soft tissue inflammatory changes adjacent to bone for subperiosteal abscess [64]. Power Doppler sonography can be used to demonstrate hyperemia surrounding a subperiosteal abscess, though it may not be positive in the early days of abscess formation [65]. Other signs associated with osteomyelitis that may be apparent at ultrasound include: fistulous communication between a subperiosteal abscess and the skin surface, swelling and edema in muscles immediately overlying the infected bone, and, in advanced cases, frank discontinuity of cortex [59, 66, 67]. Ultrasound can be very useful for detection of foreign bodies [68] (Fig. 6.11). Using ultrasound, an in vivo study of 50 patients with suspected nonradiopaque foreign bodies yielded a sensitivity of 95% and specificity of 89% for foreign body detection [69].

Because it can readily demonstrate musculoskeletal soft tissue structures and allows for accurate measurement, ultrasound has been used in a number of studies to identify correlates for degradation in biomechanical function in the diabetic foot. For example, D'Ambrogi et al. measured

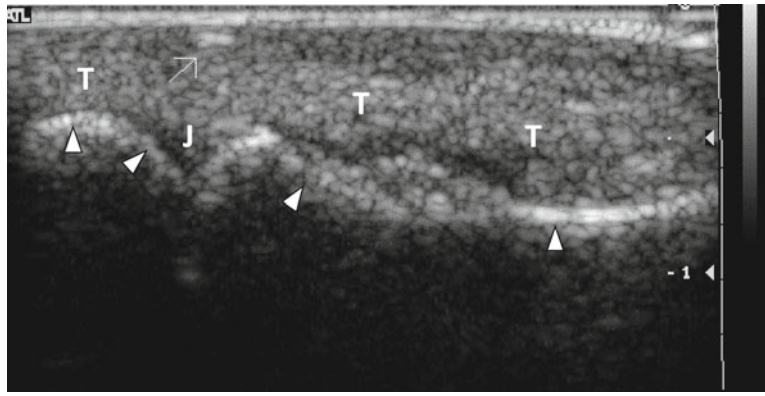

Fig. 6.11 Foreign body on ultrasound. Ultrasound image along longitudinal axis of a digit shows a small hyperechoic line (*arrow*) representing a small 12-mm foreign body. Thicker hyperechoic lines (*arrowheads*) represent the bony cortex, which obscures the underlying medullary cavity. *T* tendon, *J* joint space

the thickness of the Achilles tendon and plantar fascia in 61 diabetic patients (27 without neuropathy; 34 without) and 21 healthy volunteers and found significant thickening of the plantar fascia and Achilles tendon in the diabetic patients [70]. The abnormalities were more pronounced in neuropathic patients. Hsu and Wang et al. used ultrasound to compare the heel-pad mechanical properties in Type II diabetes patients with and without forefoot ulceration against healthy controls and found higher energy dissipation ratios when exposed to a load that simulated peak standing in-shoe plantar pressures within the heel pad of patients with Type II diabetes. They speculated that this could increase risk for developing foot ulceration [71].

Magnetic Resonance Imaging

Technique

Magnetic resonance imaging (MRI) is a primary modality for assessment of bone and soft tissue infection in the diabetic foot. Because it provides high intrinsic soft tissue contrast, MRI exquisitely depicts the full spectrum of soft tissues and can demonstrate radiographically occult bone marrow edema, without the use of intravenous contrast. Advantages of MRI over scintigraphy are precise anatomic definition and improved lesion characterization, lack of ionizing radiation, and shorter overall examination times. Because of its high sensitivity for abnormal bone and soft tissue edema and high negative predictive value, MRI can readily detect and delineate an infection's anatomic location and extent of an infection and can exclude infection when it is absent, making it a useful aid for surgical planning [9] (Table 6.4). Because of high sensitivity to marrow and soft tissue edema on MRI, however, it can sometimes be difficult to distinguish osteomyelitis and soft tissue infection from other causes of edema, such as fracture, early osteonecrosis, and reactive edema around an infection site. Postoperative changes can also cause marrow and soft tissue edema and can be impossible to distinguish from edema due to infection. MRI can be limited by artifact related to metallic hardware that can obscure the surrounding tissues. While patients with orthopedic hardware can usually be imaged, assessment of the area immediately surrounding metallic hardware is frequently limited by distortion of the local magnetic field. The extent of metal susceptibility artifact varies with the size and type of metal and can be minimized using certain imaging sequences (e.g., high-resolution

Table 6.4 Indications for MRI in detection of infection

Characterize soft tissue abnormalities
Exclude osteomyelitis
Preoperative assessment

fast or turbo spin echo sequences). Susceptibility artifact is generally more pronounced with stainless steel and less pronounced with titanium. Some, but not all, external fixation devices are MR-compatible. Some are ferromagnetic or paramagnetic and might displace in the magnetic field, so external fixation constructs must be tested for magnetic susceptibility prior to imaging. Moreover, any metal implant can result in local tissue heating, so patients with metal implants must be able to sense and communicate discomfort to the MR technologist at the time of imaging. MRI is contraindicated in patients who have pacemakers and other electronic implants, ferromagnetic cranial aneurysm clips, and intra-ocular metal. Some MRI-compatible versions of spinal stimulators and pacemakers have recently been developed, but these are not yet in common use. Most claustrophobic patients can be imaged with sedation or with the use of an open architecture magnet. The current generation of MRI machines, even when not formally described as "open" magnets, are built with shorter, wider bores ("tubes") and are often well-tolerated. Weight limitations for obese patients currently range from 300 to 450 pounds, depending on the magnet.

MRI scanners produce images using a strong magnetic field and radiofrequency (RF) waves. The magnetic field creates an equilibrium state for the atoms in the body, the RF wave perturbs the atoms, and the scanner then records how different atoms respond. Clinical magnets range in field strength from 0.2 to 3 T: the higher the field strength, the higher the potential signal-to-noise and spatial resolution (anatomic detail) in the resultant images. A variety of open, wide-bore, short-bore, and dedicated extremity magnets are now available. In order to optimally detect the signal produced by tissues in response to the radiofrequency wave perturbation and to generate high-resolution images, local RF receiver coils ("coils") are employed. Thus, for imaging the foot, a small diameter tubular extremity or foot-and-ankle coil is placed around the extremity. A typical MRI examination lasts 30–60 min, during which time approximately 4–8 imaging sequences are acquired. A sequence is a set of images designed to highlight specific tissue features and can be obtained in axial, coronal, sagittal, or any desired orientation. Some newer systems can obtain a 3D sequence that can then be reformatted into any plane. Imaging sequences are described in terms of the length of their TR (time-to-repetition) and TE (time-to-echo) times and in terms of any special radiofrequency pulses they employ (e.g., fat saturation or inversion recovery pulses). Commonly used imaging sequences are reviewed in Table 6.5. Anatomic and pathologic structures are described in terms of their signal intensity on a specific imaging sequence, often in relation to muscle. For example, fat and fatty marrow appear bright on T1-weighted images and are described as hyperintense or high signal intensity on T1-weighted images. They are low signal on fat-saturated T2-weighted and STIR sequences and are described as hypointense or low signal intensity. By contrast, simple fluid or edema is hypointense on T1-weighted images and hyperintense on T2-weighted, fat-saturated T2-weighted, and STIR sequences. Because gadolinium contrast and fat are both bright on T1-weighted images, contrast-enhanced images are often obtained using fat saturation techniques, so that fat appears darker and gadolinium contrast is bright. This is particular useful in the foot, where fatty marrow predominates. Optimal images are acquired by maximizing image signal-to-noise and using it to achieve high spatial resolution, based on appropriately small fields of view, thin slices, and smaller imaging voxel sizes. However, imaging at high spatial resolution requires longer imaging times.

Unlike CT, MRI provides high intrinsic soft tissue contrast, without the use of intravenous contrast agents. As a result, contrast is not required in order to detect changes of soft tissue infection or osteomyelitis—these processes appear as abnormal edema signal in the soft tissues and bones, respectively. However, contrast can play a role in imaging of infection in the diabetic foot by delineating soft tissue and intraosseous abscesses, highlighting fistulous tracts between ulcers and bone, and facilitating MR angiography. Gadolinium concentrates in areas of infectious or noninfectious inflammation

Table 6.5 MRI sequences—characteristics and applications

Sequence	Parameters	Use	Characteristics
T1 weighted (Fig. 6.10)	Short TE Short TR	Good for demonstrating anatomy	Normal fat and fatty marrow is bright or hyperintense on T1-weighted images
Proton density weighted	Short TE Long TR	Good for demonstrating anatomy	Similar to T1-weighted sequence, but fluid and muscle are not as dark or low signal
T2 weighted	Long TE Long TR	Fluid sensitive	Fluid and edema are bright or hyperintense on T2-weighted images, but may be hard to distinguish from fat, unless fat saturation is employed
Fat-saturated T2 weighted	Long TE Long TR ..... Fat saturation Pulse	Fluid sensitive (very)	Fluid and edema are bright or hyperintense; fat is dark or hypointense Very sensitive screen for fluid collections and for edema associated with infection or inflammation
STIR (Fig. 6.10)	Long TR Intermediate to long TE ..... Inversion recovery pulse	Fluid sensitive (very)	Normal fatty marrow is dark or low signal. Edema and fluid collections become bright or high signal Very sensitive screen for fluid collections and for edema associated with infection or inflammation, but anatomic detail is not well depicted
Fat-saturated proton density weighted	Short TE Long TR ..... Fat saturation Pulse	Fluid sensitive	Normal fatty marrow is dark or low signal. Edema and fluid collections become bright or high signal Can also screen for fluid and edema
T1 weighted with fat saturation ("fat sat") (Fig. 6.11)	Short TE Short TR ..... Fat saturation Pulse	Gadolinium contrast sensitive	Gadolinium contrast appears bright or high signal. Abscesses and proteinaceous or hemorrhagic fluid can also appear bright/high signal. Fat and simple fluid are dark or low signal Obtained both before and after IV contrast to detect contrast enhancement. Pre- and postcontrast sequences can be compared visually or computationally subtracted to demonstrate enhancing areas. Inhomogeneous fat suppression can occur When used without contrast

and produces hyperintense (bright) signal on T1-weighted images.

Most contrast agents employed for clinical MR imaging are based on the paramagnetic element gadolinium. Historically, gadolinium contrast has been better tolerated than the iodinated forms of contrast used for CT scans and catheter angiography, with lower risks of anaphylactic reactions and lower risk of nephrotoxicity. However, recently, gadolinium-based contrast media have been linked to the disease nephrogenic systemic fibrosis (NSF) in patients with severely impaired renal function [73, 74]. NSF, formerly known as nephrogenic fibrosing dermopathy, is a disfiguring and potentially disabling or fatal disorder, characterized by symmetric, coalescing, indurated skin plaques, that can also cause joint contractures and fibrosis in internal

organs. The link between intravenous gadolinium contrast and NSF is stronger for certain gadolinium formulations and seems to be dose-related [49]. Of note, follow-up dialysis after administration of gadolinium contrast does not appear to prevent NSF [74]. Due to concerns over NSF, the Federal Drug Administration (FDA) now recommends screening patients prior to administration of a gadolinium-based contrast agent to identify individuals with acute or severe chronic renal insufficiency. In our institution, this assessment is made in the MRI department, prior to contrast administration [75, 76].

Findings

On MR images, cellulitis appears as an ill-defined area in the subcutaneous fat that is of low signal on T1-weighted and high signal on STIR and T2-weighted sequences [16] (Fig. 6.2). It can be seen as both strand-like reticulate pattern of high T2 signal extending along septae between lobulaes of fat and of more confluent dense high T2 signal. However, this signal pattern is nonspecific and is common to both cellulitis and noncellulitic edema. Gadolinium administration may identify uncomplicated cellulitis, which typically shows uniform enhancement of subcutaneous edema [15].

Abscess presents as a focal lesion that is low signal on T1-weighted images and high signal on T2-weighted and STIR images. Without intravenous gadolinium, an abscess may not be distinguishable from dense soft tissue edema seen in severe cellulitis or from soft tissue phlegmon [72]. Following administration of intravenous gadolinium, an abscess demonstrates peripheral or rim enhancement, demarcating the fluid collection within (Fig. 6.12). The enhancing rim is believed to correspond to granulation tissue in the pseudocapsule. However, rim enhancement is a sensitive but nonspecific sign for abscess and can be seen in necrotic tumors, seromas, ruptured popliteal cysts, and hematomas [72]. Pus in the center of the abscess can have variable signal intensity, depending on its contents. Simple fluid will have low T1/high T2 signal, but abscesses often have high T1 signal content due to the presence of proteinaceous material within the fluid. Like proteinaceous fluid, hemorrhage can also appear high signal on T1-weighted images. Because this high T1 signal intensity appearance could be mistaken for gadolinium enhancement, comparison of pre- and postcontrast images becomes essential.

The diagnosis of septic arthritis is generally made clinically and confirmed by percutaneous joint aspiration or surgery [15]. The MR appearance of septic arthritis consists of joint effusion, often with synovial thickening, intra-articular debris, and surrounding reactive marrow and soft tissue edema. Following administration of intravenous gadolinium, there is intense synovial enhancement. Periarticular reactive marrow edema may demonstrate gadolinium enhancement even in the absence of osteomyelitis [15]. This constellation of findings is suggestive, but not specific for, infection and can also be seen in inflammatory conditions such as rheumatoid arthritis and seronegative arthropathies.

The primary MRI finding in osteomyelitis is abnormal marrow signal that enhances [72]. The abnormal marrow appears low signal (dark) on T1-weighted images and high signal (bright) on fluid-sensitive images such as fat-saturated T2-weighted and STIR images, typically with ill-defined margins (Fig. 6.1; Table 6.6). Changes in marrow signal intensity can be detected as early as 1–2 days after onset of infection [25, 77]. Following intravenous administration of gadolinium contrast, the abnormal marrow enhances and is seen as a bright area on the fat suppressed T1-weighted images. Secondary signs of osteomyelitis include cortical interruption, periostitis (seen as enhancement at the margins of the periosteum), and a cutaneous ulcer or sinus tract in contiguity with the abnormal marrow [15, 78]. Contrast does not identify new areas of signal abnormality compared with fat-saturated T2-weighted or STIR sequences [77]. Rather it helps demonstrate soft tissue and intraosseous abscesses and outline fistulous tracts between osteomyelitis and the skin [77]. It can also distinguish joint fluid from thickened synovium. Morrison et al. reported improved sensitivity and specificity for detection of osteomyelitis, using gadolinium contrast—88% sensitivity and 93%

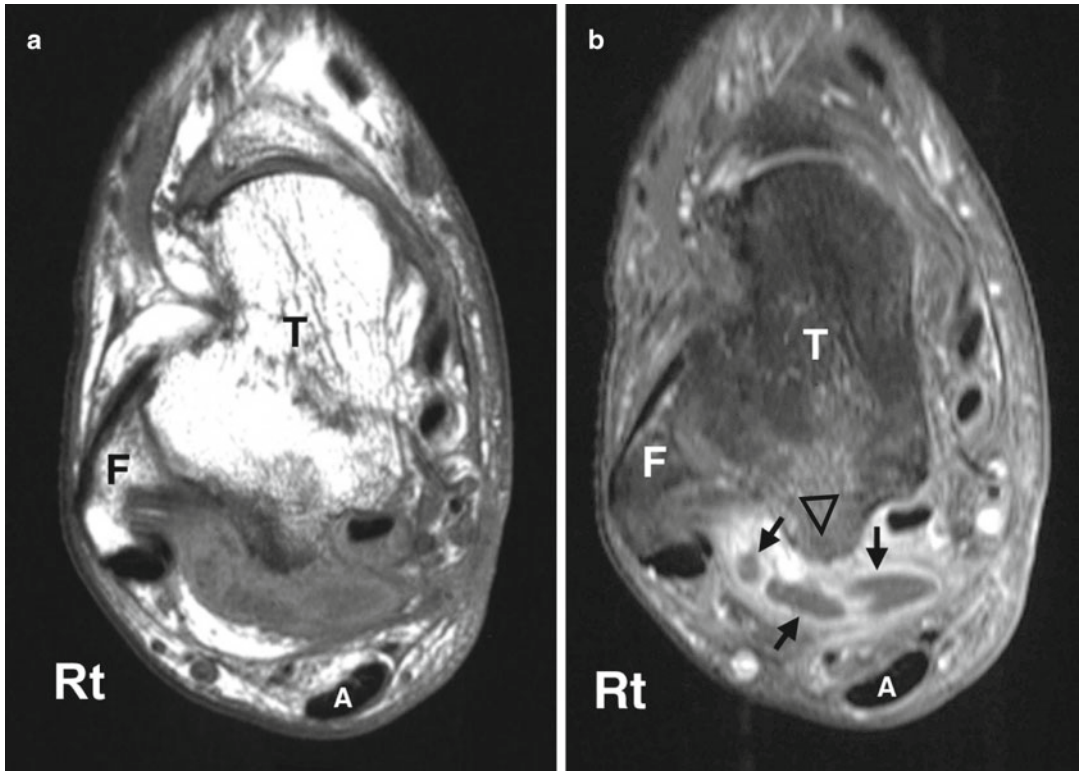

Fig. 6.12 Soft tissue abscess on MRI. Axial images of the ankle in a diabetic patient with ankle swelling. T1-weighted image (**a**) shows abnormal low signal posterior to the talus. Fat suppressed T1-weighted image (**b**) was obtained after IV administration of gadolinium. Note the bright enhancing peripheral rim (*arrows*) surrounding the abscess. The rim is slightly thickened. Central nonenhancement confirms fluid content. Enhancement is also seen in the adjoining portion of the talus and the intervening talar cortex is thinned and irregular (*open arrowhead*). Because they abut the abscess, these findings in the bone are highly suggestive of osteomyelitis. *A* Achilles, *F* fibula, *T* talus

Table 6.6 MRI findings of osteomyelitis

Primary signs
Hyperintense (bright) marrow signal on STIR sequence
Hypointense (dark) marrow signal on T1-weighted sequence
Enhancing marrow on postcontrast T1-weighted sequence
Secondary MR signs
Periosteal reaction
Subperiosteal abscess
Periostitis (manifested by periosteal enhancement)
Cortical destruction
Ulcer
Sinus tract

specificity for contrast-enhanced studies versus 79% sensitivity and 53% specificity for noncontrast-enhanced images [72]. Sensitivity and specificity of various secondary signs for identifying osteomyelitis were: sinus tracts (32%/85%), cellulitis (84%/30%), soft tissue abscess (26%/74%), ulcers (41%/81%), cortical tract or disruption (86%/78%) [78]. A negative MRI effectively excludes osteomyelitis (Fig. 6.3) [79].

The sensitivity and specificity of MRI for detection of osteomyelitis compiled from five studies is 96% and 87%, respectively [80–84].

Sensitivities and specificities for detection of osteomyelitis in diabetics are lower, respectively, 82% and 80%, in large part due to neuroarthopathic changes [72, 85]. Ahmadi et al. identified features that can help to distinguish between osteomyelitis and neuropathic arthropathy. They examined 128 neuropathic joints in 63 patients and concluded that features more indicative of infection were sinus tract, replacement of soft tissue fat, fluid collection, or extensive marrow abnormality, while features indicative of neuroarthropathy without infection were a thin rim of peripheral enhancement around an effusion, the presence of subchondral cysts, or the presence of intra-articular loose bodies.

Because of its high negative predictive value, MRI can facilitate accurate depiction of the maximum possible extent of marrow involvement by osteomyelitis. As such, MRI can help for planning of foot-sparing surgical procedures [72]. Marrow involvement is well-demonstrated on fluid-sensitive images, such as fat-saturated T2-weighted or STIR sequences.

Its advantages notwithstanding, MRI has several important limitations. MRI of the infected diabetic foot yields a significant number of false-positive diagnoses. The kind of abnormal marrow signal associated with osteomyelitis can also be seen with neuroarthropathy, including silent bone stress injuries associated with diabetic neuroarthropathy, bone contusions, fractures (Figs. 6.13 and 6.14), and, occasionally, osteonecrosis. The hyperemic phase of osteoarthropathy may display enhancing marrow edema indistinguishable from osteomyelitis. Intense soft tissue inflammation may also give rise to reactive edema in the adjoining bone, in the absence of osteomeylitis. False-negative contrast enhancement can occur in the setting of vascular insufficiency [86]. The utility of MR imaging for following response to treatment of osteomyelitis remains to be defined. Due to its high sensitivity for detection of soft tissue and marrow edema, MRI findings can be expected to lag behind the clinical response in treatment of soft tissue infection and osteomyelitis. As noted

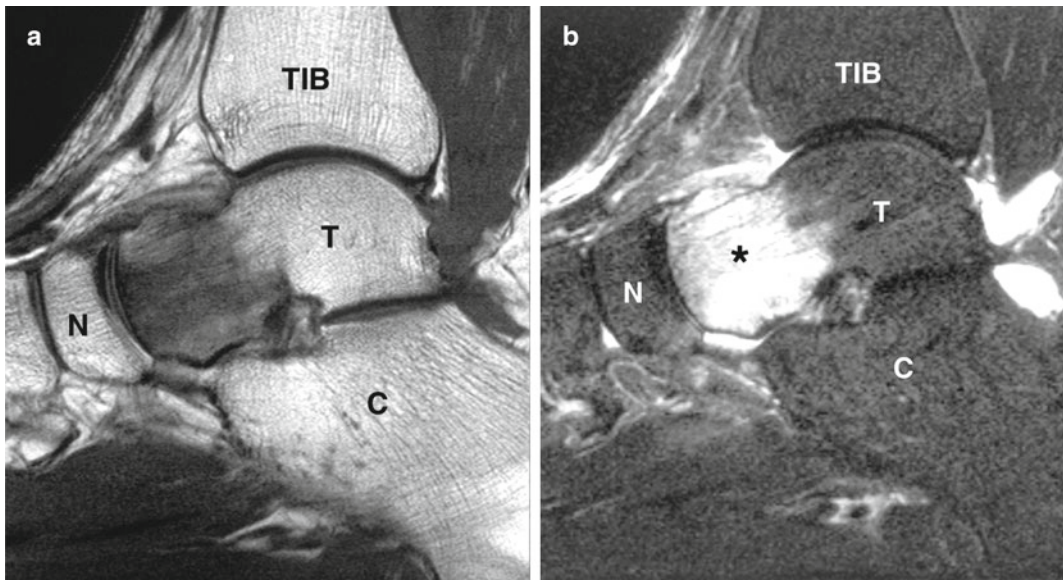

Fig. 6.13 Marrow edema on MRI. Sagittal images of the ankle show marrow edema (*asterisk*) which is (**a**) dark on T1-weighted image and (**b**) bright on STIR images. This marrow edema pattern is nonspecific and is similar to the marrow changes in osteomyelitis. However, this patient sustained trauma to the anterior talus and, here, the marrow edema represents a bone bruise. Specificity and accuracy can be improved by administration of gadolinium, as osteomyelitis frequently shows marrow enhancement. *C* calcaneus, *N* navicula, *T* talus, *TIB* tibia

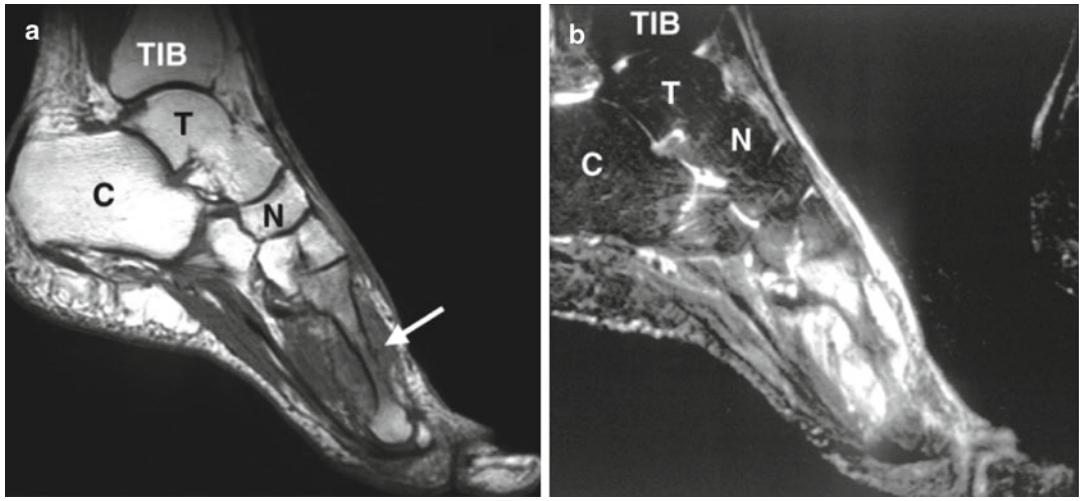

Fig. 6.14 Stress fracture on MRI. Sagittal T1-weighted (**a**) and STIR (**b**) MR images of the foot demonstrate cortical irregularity of the mid-diaphysis of the metatarsal bone (*arrow*). The marrow signal is abnormal, consistent with a marrow edema pattern: low signal on the T1-weighted image and high signal on the fluid-sensitive STIR image. The fracture line (*arrow*) remains dark on both sequences and is surrounded by bright edematous marrow on the STIR image. Marked soft tissue swelling surrounding the fracture is also better appreciated on the STIR images (**b**). *C* calcaneus, *N* navicular, *TIB* tibia, *T* talus

above, the use of gadolinium contrast in patients with severe renal failure is now a contraindication to gadolinium.

In addition to assessment of bone and soft tissue infection, there is great interest in the use of anatomic MRI [87–89], MR spectroscopy [90–92], and MR elastography [93] to identify early changes of structural and metabolic pathology in the diabetic foot.

Angiography

Angiography is indicated in diabetic patients with nonhealing ulcers or osteomyelitis who require mapping of vascular disease prior to endovascular or surgical treatment. Almost without exception, patients with nonhealing foot ulcers will have severe steno-occlusive disease involving all three runoff vessels of the calf (anterior tibial, posterior tibial, and peroneal arteries). In this patient population, 20% of peripheral bypass grafts will have to extend to a pedal artery. The distal anastamosis is either to the dorsalis pedis artery or to the proximal common plantar artery trunk [94]. Thus, detailed mapping of arterial disease from the abdominal aorta to the pedal vessels is necessary.

Several alternative—and, in some cases, complementary—techniques currently exist for mapping the vessels in the diabetic foot: conventional and digital subtraction angiography (DSA), MR angiography, CT angiography, and duplex Doppler ultrasound. These techniques are reviewed below. In general, vascular disease in diabetics tends to predilect the smaller caliber vessels of the distal lower extremity, which poses special challenges for imaging.

Catheter Angiography—Conventional and Digital Subtraction Angiography

Traditionally, vascular imaging has been performed using conventional angiography [95]. Conventional angiography is an invasive procedure, performed in the angiographic suite under fluoroscopic (real-time X-ray imaging) guidance. A thin, flexible catheter is inserted into the aorta or arteries, usually via a femoral artery approach. A relatively large bolus of iodinated contrast is injected into the intra-luminal catheter and rapid

sequence radiographs are exposed. Although examination of the abdominal aorta and iliac vessels can readily be performed with a multiside-hole catheter in the abdominal aorta, examination of the femoral, popliteal, tibioperoneal, and pedal arteries entails placement of a catheter in the ipsilateral external iliac artery. Selective catheter placement has the advantage of limiting contrast burden in a patient group predisposed to renal insufficiency.

Digital subtraction angiography (DSA) has replaced the older form of hardcopy, cut-film angiography in most institutions [49]. DSA is particularly advantageous for imaging diabetic arterial disease, because it is superior in terms of demonstrating small caliber distal vessels and uses less contrast to do so. In DSA, a set of images of the limb is obtained prior to administration of contrast (known as a "mask") and stored electronically. AP and lateral images are then obtained during administration of contrast, along the length of the vessels of interest, including one perpendicular to the interosseous membrane, that separates out the anterior tibial and peroneal vessels. Pre- and postcontrast image sets are subsequently subtracted by the computer to generate a final DSA image set that shows the intra-arterial contrast map. (Fig. 6.15). Using DSA, the interventionalist can perform rapid road-mapping of the vasculature during a procedure, without having to wait for hardcopy films to be developed. Nonionic iso-osmolar contrast agents, although more expensive, are typically used because they are associated with less pain and a lower risk of contrast-induced nephropathy, a risk that is higher in diabetic patients [96]. Newer high-resolution flat panel image intensifiers can cover larger fields of view and facilitate fewer injections and decreased radiation exposure. Portable and surgical suite DSA systems are available.

Conventional angiography, including DSA, remains the gold standard for arteriographic imaging. The major advantage of conventional angiography is that it provides access to perform not only diagnostic but also therapeutic, vascular procedures, including angioplasty, atherectomy, stenting, and thrombolysis. A well-timed study can provide very high spatial resolution images of small vessels. The major risks of the DSA angiography include radiation exposure, potential for bleeding, injury to the vessel wall, dislodgment of embolic material, and risk of renal failure or allergic reaction from the iodinated contrast. Injury to the femoral artery access site can be decreased with the use of lower profile catheters and sheaths and the use of ultrasound-guidance for placing the catheter [49]. Not infrequently, vascular disease and slow flow can disrupt the timing of the examination, with resultant failure to demonstrate the distal vessels. This is especially problematic when demonstration of distal vessels is the key to planning a bypass graft procedure. Good technique is a key for successful opacification of the distal tibial and pedal arteries.

There are several strategies for reducing contrast in exposure in patients with renal insufficiency: (1) if the femoral pulse is normal, a choice may be made to limit angiographic imaging to the extremity itself, and forgoing examination of the aortoiliac arteries; (2) the catheter can be advanced distally, into the distal superficial femoral or popliteal artery, for the injection, instead of performing the injection proximally, in the external iliac artery; (3) full strength contrast can be diluted with normal saline; (4) carbon dioxide (CO_2) can be used, instead of iodinated contrast for examination of the aorta and pelvis [49].

MR Angiography

More recently, MRI has come to play a role in the imaging of arterial disease, in the form of MR angiography (MRA). MRA has the benefit of providing detailed anatomic mapping of arterial disease while, at the same time, obviating the need for arterial catheter placement and associated complications. Contrast-enhanced MRA (CE-MRA) and noncontrast-enhanced time-of-flight (TOF) MRA are the most commonly used techniques for performing MRA of the lower extremity [97, 98] (Figs. 6.16 and 6.17). Phase-contrast MRA, an alternative noncontrast-enhanced MRA technique, has not been in common use, but is being currently being revisited and new noncontrast-enhanced techniques are also being developed. Gadolinium, the contrast

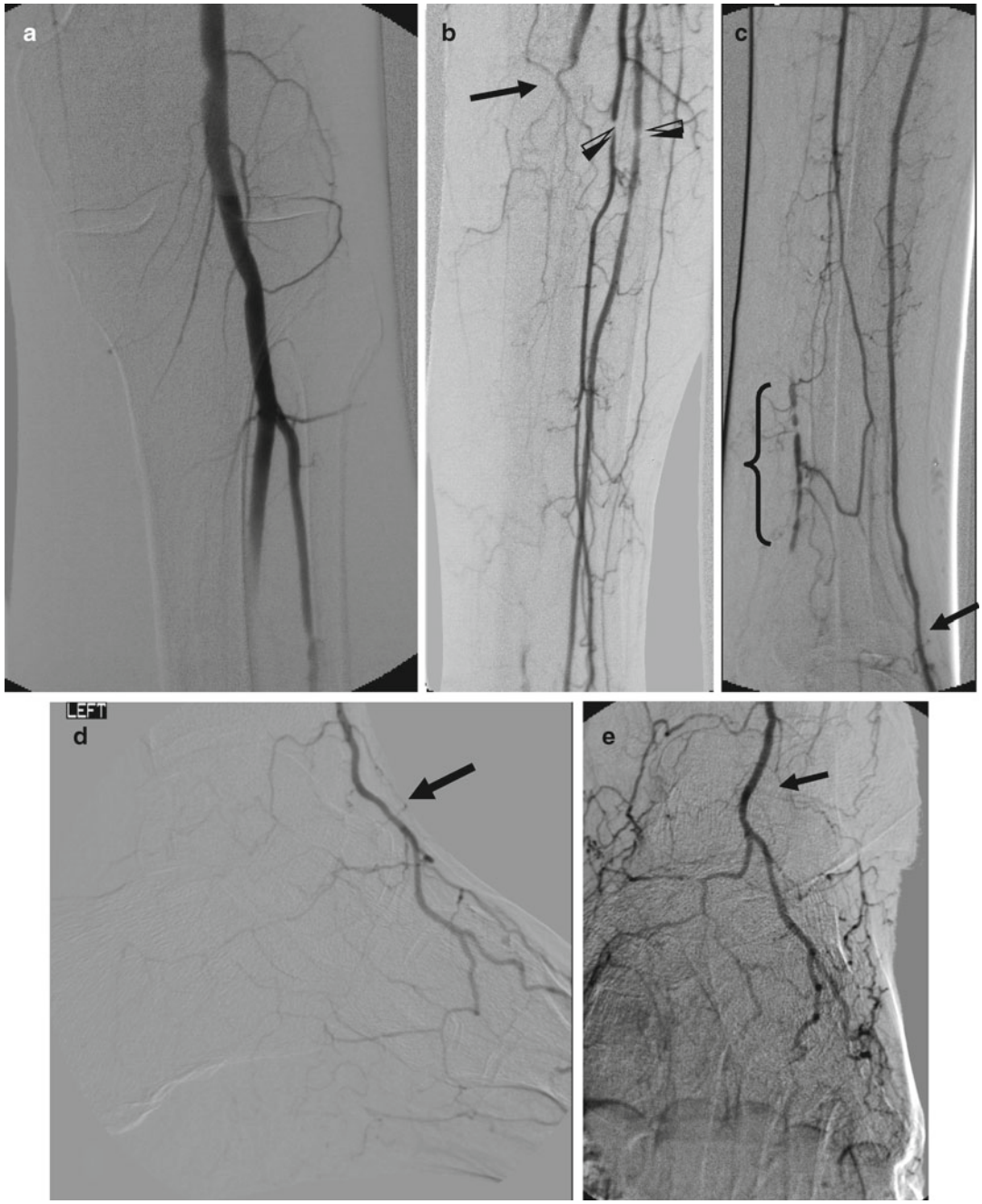

Fig. 6.15 Digital subtraction angiogram (DSA) of the lower extremity in 74-year-old diabetic man with non-healing heel ulcer. (**a**) Images demonstrate a patent popliteal artery, anterior tibial artery, and tibioperoneal trunk. (**b**) The posterior tibial artery is occluded (*arrow*) and there are stenoses in the proximal anterior tibial and peroneal arteries. (**c**) Just above the ankle, the left peroneal artery is occluded and there is reconstitution of a short diseased posterior tibial artery (*bracket*) from collateral vessels. The dorsalis pedis (DP) artery is patent (*arrow*). (**d**, **e**) Images in the foot show patent DP (*arrows*)

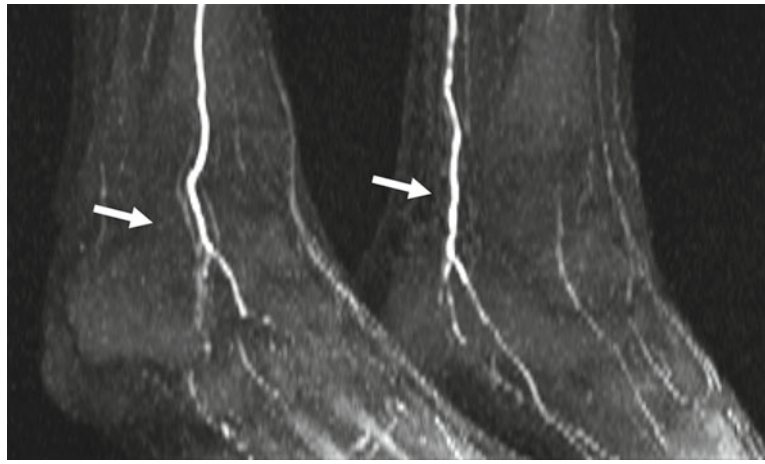

Fig. 6.16 Time-of-flight MR angiogram in the ankle and foot demonstrates single-vessel runoff, with patency of the posterior tibial artery and portions of the plantar arteries on both sides (*arrows*)

agent used in MRA, has traditionally been favored over the iodinated contrast used for catheter angiography, because of a lower incidence of allergic reaction and contrast-induced nephrotoxicity. However, new concerns regarding an association between gadolinium administration in patients with renal failure and development of a disease called NSF have arisen.

Time-of-flight MR angiography relies on a noncontrast-enhanced, flow-sensitive MR sequence. Computer postprocessing of the MR data generates coronal, sagittal, or oblique reconstructions that mimic the appearance of conventional angiograms. TOF MRA can be time consuming, requiring 1–2 h to cover the distance from the aortic bifurcation to the distal lower extremity. Cardiac gating of the MR images improves image quality, but lengthens examination time, especially when the patient has a cardiac arrhythmia or is on beta-blocker medication. TOF MRA images tend to exaggerate the degree of steno-occlusive disease and are prone to motion and metallic susceptibility artifact.

Gadolinium- or contrast-enhanced MRA (CE-MRA) relies on intravenous injection of a small volume of gadolinium contrast and rapid imaging that is timed to optimally follow the passage of the contrast bolus through the arteries. This technique has the advantage of short scan time, reduced motion, and reduced susceptibility artifacts. It is more accurate than TOF MRA examination in depicting the grade of steno-occlusive disease and offers higher resolution in the distal arteries of the lower extremity [99, 100]. CE-MRA uses a much smaller volume of contrast than conventional angiography and therefore generates a smaller osmotic load and subsequently a lower incidence of nephrotoxicity. However, visualization of the arteries can be limited by venous enhancement (Fig. 6.17) or by suboptimal arterial filling related to inaccurate timing of data acquisition. Use of new rapid image data-sampling techniques for CE-MRA, such as TRICKS (time-resolved imaging of contrast kinetics), can help improve imaging of arteries in the foot. Specifically, these kinds of sequences help address problems with proper timing of the contrast bolus and reduce "venous contamination" of images, while improving conspicuity of small distal vessels.

In general, MR angiography achieves sensitivities of 92–97% and specificities of 89–98% [101, 102] and compares favorably to conventional angiography. Both TOF and CE-MRA can reveal patent arteries not seen on conventional arteriograms [103, 104]. 3D CE-MRA is superior to 2D TOF MRA for detection and grading of peripheral arterial disease [104, 105]. Dorweiler et al. [106] examined the performance of pedal bypass grafts to foot vessels that were detected

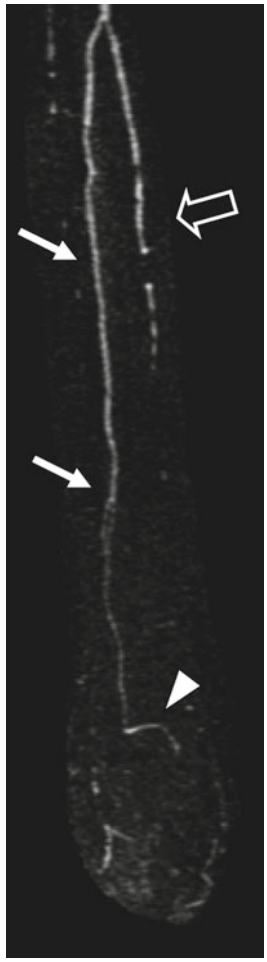

Fig. 6.17 Contrast-enhanced MRA for nonhealing ulcer. There is single-vessel runoff via the peroneal artery (*arrow*), to the level of the ankle joint, with reconstitution of an attenuated dorsalis pedis artery (*arrowhead*) via collaterals. The proximal posterior tibial artery demonstrates multiple stenoses and is occluded in the mid-calf (*open arrow*)

by MRA, but occult at conventional angiography, in 15 patients with diabetes mellitus and severe arterial occlusive disease [106]. During 22-month mean follow-up, there was one perioperative graft occlusion and one major amputation, resulting in a secondary patency rate of 93.1% and a limb salvage rate of 89.5% at 36 months. The appropriate clinical role of MRA in the management of arterial disease in the diabetic foot is debated [107].

Computed Tomographic Angiography

Lower extremity or peripheral computed tomographic angiography (CTA) is a relatively new technique for evaluation of the peripheral arterial tree. With the advent of multidetector CT (MDCT) in 1998, CT imaging became fast enough to allow scanning of inflow and runoff vessels in the entire lower extremity, with sufficient spatial resolution, in a single CT acquisition. The acquisition time for these images is on the order of less than 1 min [104]. The minimum number of channels required to generate a peripheral CT angiogram is provided by a 4-detector scanner, but later 16- and 64-detector machines are preferred, because they provide near-isotropic 3D image sets, allowing reformatting of high-quality images in any plane [104, 108]. Images are generated using standard intravenous CT contrast, injected into an antecubital vein via power injector. Sophisticated scanning protocols are employed to optimize opacification in the arteries of interest and the scanner table is moved during the scan to "chase" the contrast bolus. As with conventional angiography, optimal timing of the contrast bolus is affected by cardiac function and by delays due to arterial pathology in the infrarenal aorta and lower extremity arteries. Venous enhancement may contaminate arteriograms when there is significant arteriovenous shunting or when longer scan times are used, but, with good technique, this should rarely pose a diagnostic problem [104]. Artifactual narrowing or occlusion of the dorsalis pedis artery ("ballerina sign") can occur with excessive plantar flexion of the foot, as it can with other forms of angiographic imaging [109]. CTA involves a relatively high radiation dose [110] and requires large volumes of contrast (150–180 CC) per run.

Once the initial CT angiographic images are acquired (Fig. 6.18a), the data associated with those images can be postprocessed in order to generate clinically useful images (Fig. 6.18b–g), but this postprocessing requires a high level of expertise, in order to avoid introducing postprocessing artifacts that will degrade diagnostic accuracy. In some institutions, CT angiogram studies are postprocessed by specially trained

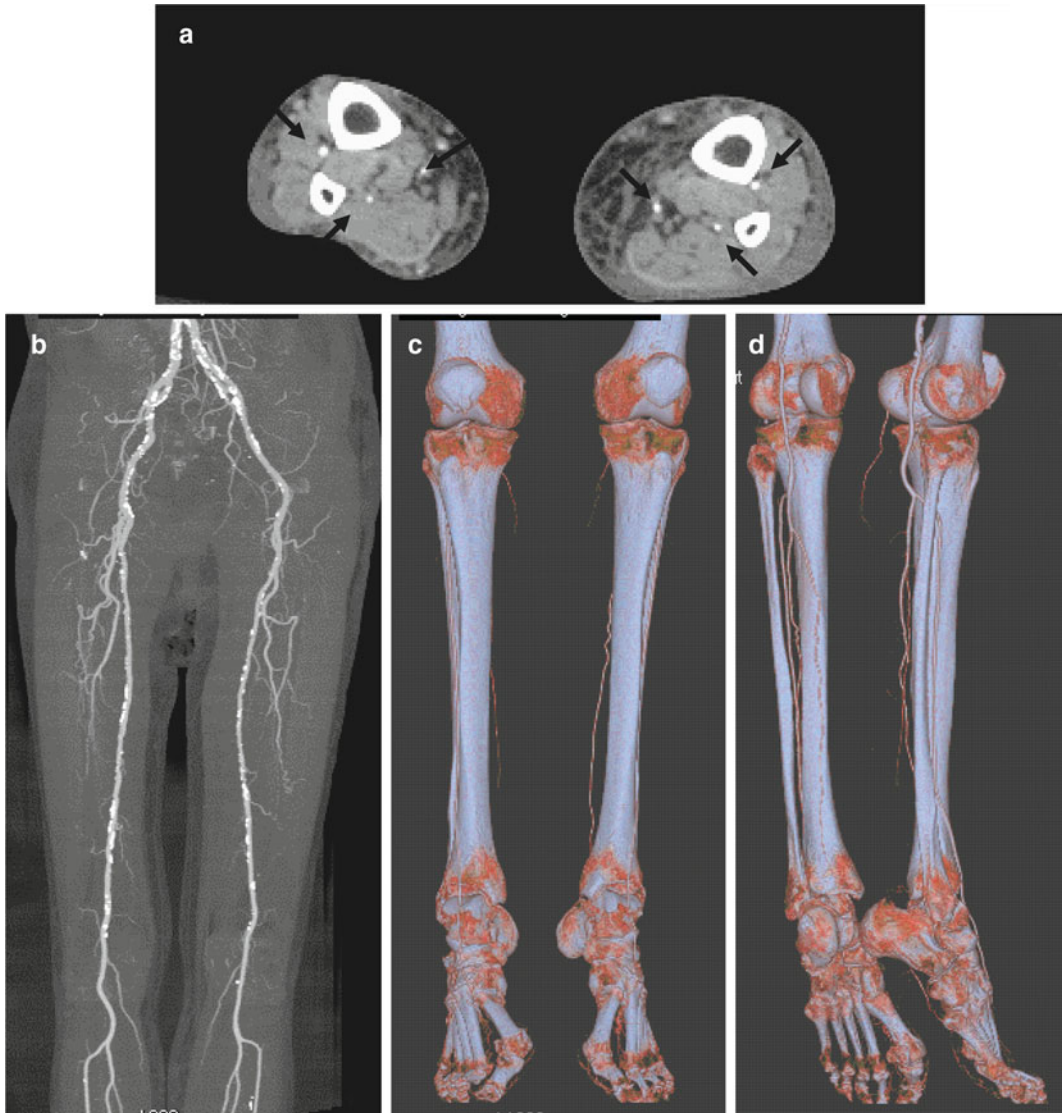

Fig. 6.18 CT angiogram with patent vessels in woman with concern for claudication. (**a**) Axial image of both lower extremities from a CT angiogram represents the source image for subsequent computer-generated postprocessed images. All three lower extremity runoff vessels are patent bilaterally, seen as small bright foci (*arrows*), due to administered contrast. (**b**) Maximum intensity projection (MIP) image was generated in the image processing lab from a stack of source images similar to (**a**) acquired through the lower body. The MIP mimics a conventional arteriographic display. Bilateral 3 vessel runoff (proximal portion) is well depicted. Based on the protocol, images can be extended distally. Scattered areas of higher density (whiter) seen along the vessels reflects the presence of calcified atherosclerotic plaque. (**c**) AP and (**d**) oblique volume rendered (VR) images display the vessels in relation to bony anatomy, based on Hounsfield unit density thresholds. (**e**–**g**) Curved planar reformatted images can be generated along the actual path of the vessel, in order to lay out the vessel in a single plane, respectively, depicting the anterior tibial, peroneal, and posterior tibial arteries

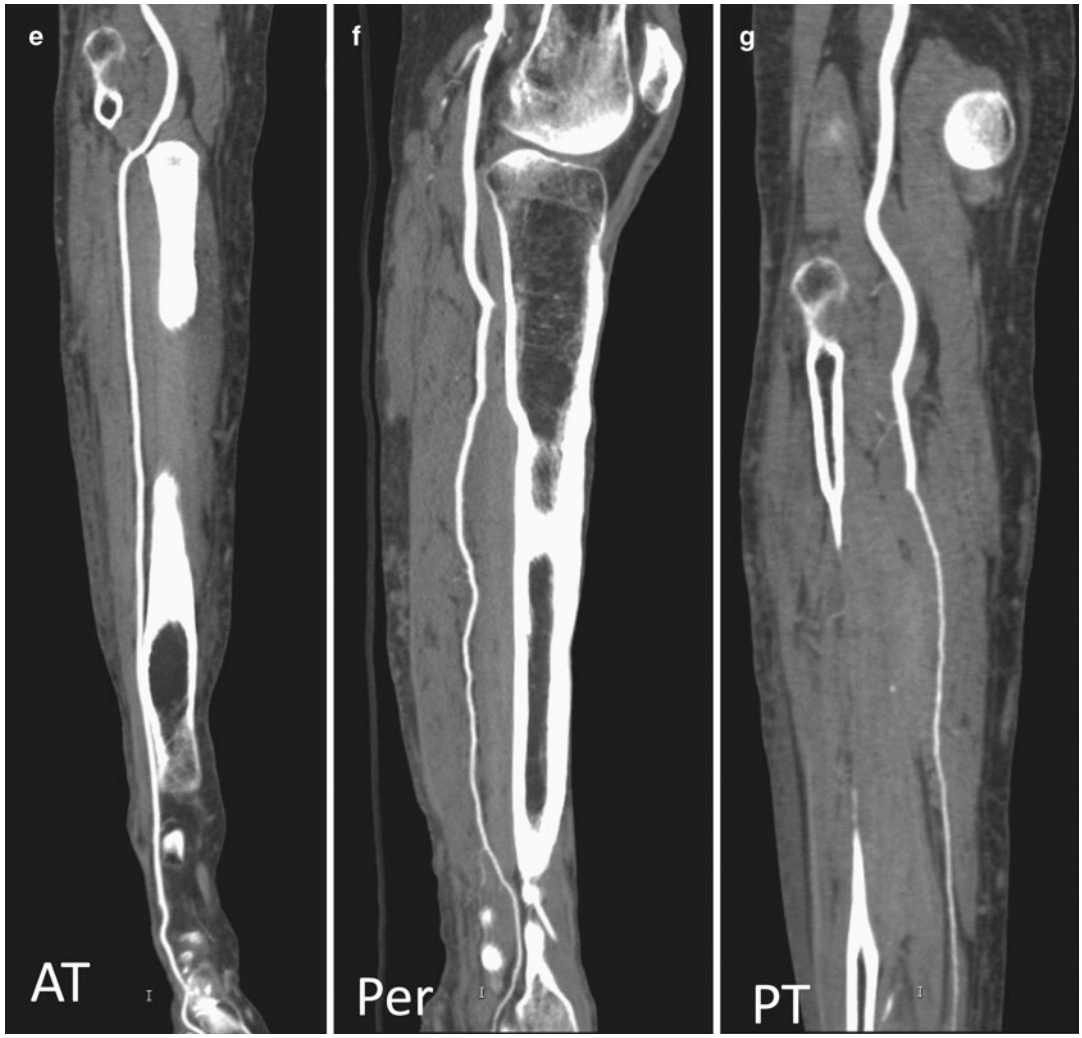

Fig. 6.18 (continued)

technologists in a dedicated image processing lab. Postprocessing techniques include MIP images, which mimic conventional angiography displays (Fig. 6.18b). These require subtraction of bone from the image, at which time there is a risk of inadvertently removing vessels adjacent to bone. Volume rendering (VR) represents a form of 3D surface display that does not rely on subtraction of bone from the image (Fig. 6.18c, d). In VR, however, vessels can be inadvertently removed by choice of VR parameters. In both MIP and VR techniques, stents and vessel calcifications can completely obscure the vessel lumen, making it difficult or impossible to assess flow in that segment—this can limit the utility of CTA in approximately 60% of patients with peripheral arterial occlusive disease [108]. In these cases, source images obtained perpendicular to the vessel can be useful. Curved planar reformations (CPRs), which are longitudinal cross sections generated along a predefined vascular center line, can be generated along the length of the vessel, regardless of its course (Fig. 6.18e–g), but they require manual or semiautomated tracing of the vessel center line. With CPRs, artifacts mimicking vessel stenosis or occlusion can occur when

the center line is not selected properly. When viewing CTA images, regardless of postprocessing technique, care must be taken not to overestimate stenosis or occlusion due to artifactual "blooming" of calcifications or stents on narrow viewing windows. A viewing window of at least 1,500 HU may be required [104]. Of note, when there is extensive vascular calcification in smaller crural or pedal arteries, it may be impossible to resolve the vessel lumen, notwithstanding proper window/level selection [104].

There is limited data available for assessment of the diagnostic accuracy of CTA in the evaluation of peripheral arterial occlusive disease. Wilmann et al. examined the use of submillimeter collimated 16-channel MDCT in 39 patients and found sensitivity of 96% and specificity of 97%, even in popliteo-crural branches, using an effective radiation dose that was lower than for conventional DSA [111]. To date, use of CTA for assessment of pedal arteries has not been reported. As suggested above, dense vascular calcification can potentially reduce diagnostic performance on MDCT [104, 112].

Doppler Ultrasound

In addition to its ability to provide gray-scale anatomic imaging, ultrasound can play an important role in depicting blood flow [113]. Three complementary techniques for blood flow imaging with ultrasound exist: (1) duplex Doppler ultrasound; (2) color flow imaging; and (3) power Doppler. These techniques are based on the Doppler effect: when a sound beam is reflected back off a moving object, the frequency of the sound beam is altered, increasing in frequency when the object (here, red blood cells) is moving toward the source of the sound beam, and decreasing when the object is moving away. The change in frequency is proportional to the velocity of the object and is greatest when the sound beam travels parallel to the vessel. Because Doppler measurements capture information about the velocity of blood flow, quantitative assessment of the severity of stenosis can be obtained, based on peak systolic and end-diastolic velocity measurements. Higher peak systolic measurements indicate more severe stenoses [114]. Using this technique, stenosis is graded as the ratio of peak systolic velocity of the target vessel divided by [the velocity in the adjacent nonstenosed vessel minus the peak systolic velocity ratio]. Findings are recorded on an anatomic diagram, creating a visual map of the vascular pathology. Doppler wave form analysis refers to depiction of the *pattern* of arterial blood flow, based on Doppler frequency shift. Patent arteries show a normal triphasic flow pattern. However, with increasing stenosis, the wave form flattens (Fig. 6.19). In duplex Doppler, the gray-scale ultrasound image of the vessel and the vascular waveform are depicted together (Fig. 6.20). Duplex Doppler ultrasound can be used to image arteries and veins, to assess the severity and extent of peripheral artery disease, and to identify pedal arteries for bypass. Color Doppler images depict the frequency shift data as a color spectrum that encodes both directional and velocity information. In color Doppler images, red and blue colors are superimposed on gray-scale anatomic images of vessels, to indicate, respectively, flow toward and away from the transducer. Color Doppler images are often used in conjunction with duplex Doppler to aid in visualizing vessels. Doppler measurements and resultant images may be degraded by aliasing artifacts, either when the sampling frequency is too low or the angle of incidence between the sound beam and the vessel are too low. The third technique, power Doppler, is more sensitive to blood flow than color Doppler, allowing it to show smaller vessels and slower flow rates. Power Doppler scans assign color to flow, independent of its direction. Because of its high sensitivity, power Doppler can demonstrate flow associated with inflammation and neovascularity, such as inflammation associated with soft tissue infection and in soft tissues adjacent to osteomyelitis. Power Doppler can also help to distinguish between phlegmon and abscess, based on the lack of flow within the center of an abscess. With power Doppler, artifactual "flow" can occur with movement of the transducer or body part and false-positive and -negative findings can occur if the ultrasound machine's settings (color gain) are not properly set.

Doppler

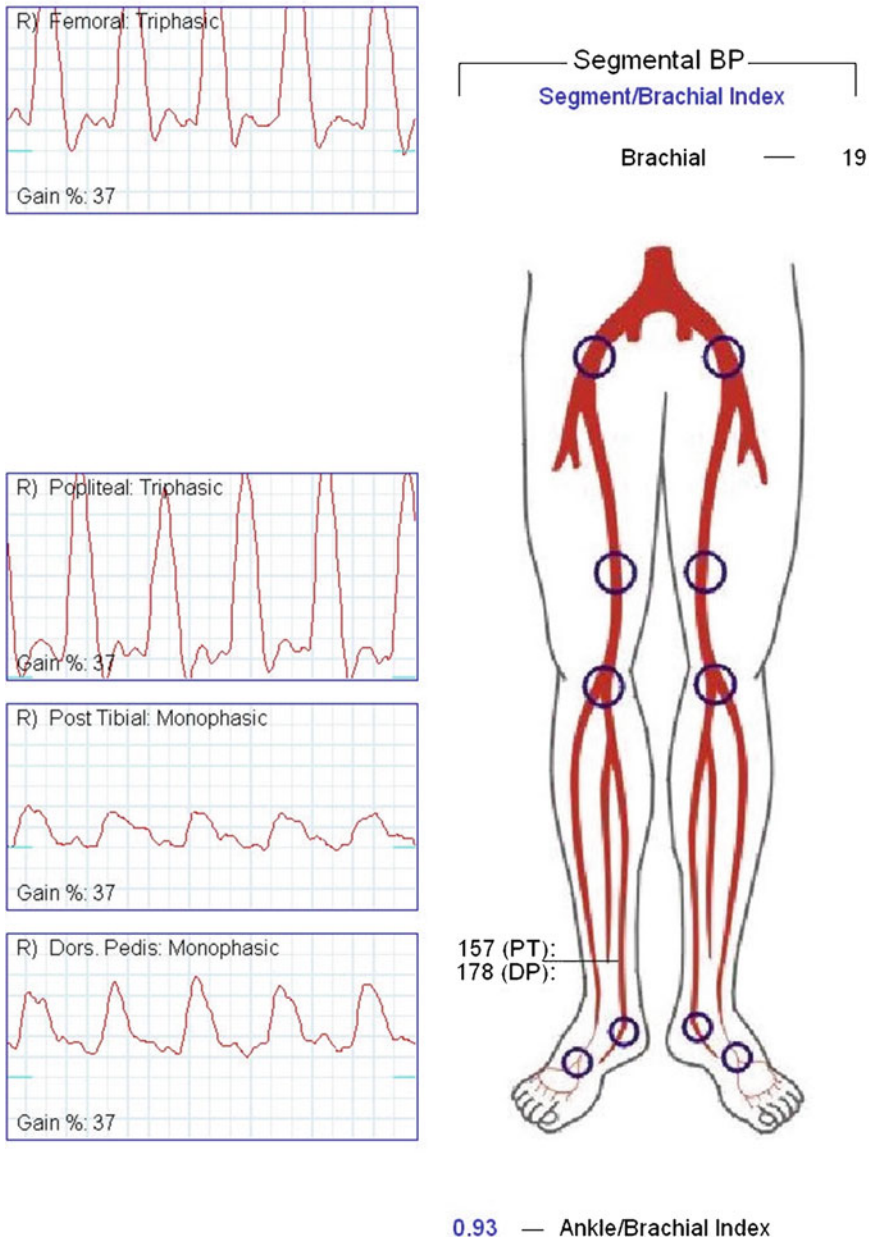

Fig. 6.19 Doppler wave from analysis in 62-year-old with right great toe ulcer and cellulitis. Arterial waveforms were evaluated using Doppler ultrasound at standardized sites along the ipsilateral lower extremity. While a normal triphasic wave pattern was observed in the femoral and popliteal vessels, a monophasic wave pattern was observed in the posterior tibial and dorsalis pedis vessels, indicating intervening stenosis

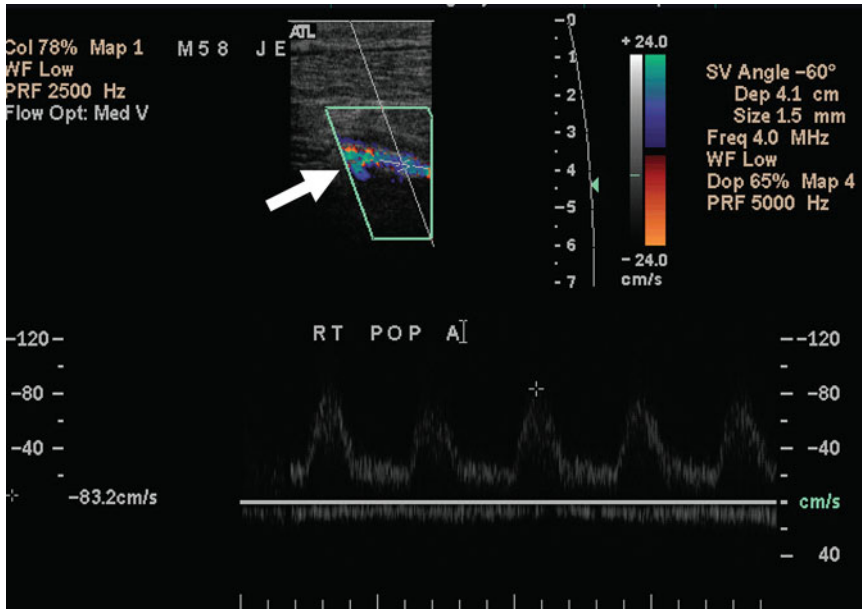

Fig. 6.20 Duplex Doppler examination at popliteal artery. The gray-scale ultrasound image of the popliteal artery (*thick arrow*) is used to position the cursor for the measurement. Here, Color Doppler is being superimposed on the vessel to help highlight the artery and arterial flow velocities. The popliteal artery waveform generated by the measurement is shown below. A cursor is placed at the height of the waveform peak (*thin arrow*) and yields a peak flow rate of 83 cm/s, with no evidence of stenosis. Duplex Doppler ultrasound can be used to generate data like this long the length of a vessel, in order to map the site, length, and severity of stenoses

Advantages of Doppler ultrasound are similar to those of ultrasound in general: the examination is noninvasive, avoids the hazards of an arterial puncture, does not require ionizing radiation or administration of nephrotoxic or allergenic contrast agents, and is generally well-tolerated by a variety of patients. Ultrasound is also less costly than preprocedure diagnostic angiography. Disadvantages of Doppler ultrasound include: operator dependence of the examination, relatively lengthy examination time, and limited ability to ensure that the entire area of interest has been imaged [104]. Mural calcification can cause acoustic shadowing and interfere with accurate measurement [115]. In practice, accurate Doppler measurements require a vascular laboratory with sufficient experience and attention to quality control. In the future, the use of ultrasound intravascular agents may contribute to improved imaging, but clinical utility of these techniques in the diabetic foot remains to be established [116].

Duplex ultrasound examination can be used for noninvasive preoperative planning of re-vascularization procedures in diabetic patients [115, 117]. Ultrasound can be used to map occlusions for length and stenosis, based on velocity profiles [115]. Though a complete discussion of the field is beyond the scope of this chapter, a number of studies have demonstrated the utility of duplex Doppler ultrasound in this setting. Doppler ultrasound interrogation can be performed with high degree of sensitivity and specificity in aortoiliac and femoropopliteal segments [117]. Duplex imaging of tibial vessels requires greater operator skill than imaging of larger, more proximal vessels, but can reliably identify stenosis and occluded segments and, in some cases, may be superior to angiography [118]. Hofmann et al. examined the use of preoperative high-frequency duplex scanning of potential pedal target vessels [119]. They studied 33 consecutive diabetic patients suffering from critical limb ischemia,

with indications of infra-popliteal occlusive disease, using a 13 MHz ultrasound probe, and attempted to identify the pedal target vessel best suited for surgery, based on inner diameter, degree of calcification, maximal systolic velocity, and resistive index. Results of Duplex scanning were compared with (1) results of selective digital subtraction arteriography (DSA) and contrast-enhanced MRA interpreted by two radiologists; (2) the site of distal anatamosis predicted by a vascular surgeon based on the MRA and DSA; (3) the definitive side of distal anastamosis; and (4) early postoperative results. They found that Duplex scanning depicted significantly more pedal vascular segments than selective DSA, with relatively high agreement between the duplex ultrasound prediction and the definitive site of anastamosis (kappa 0.82). Levy et al. examined 105 consecutive lesions angioplastied among 56 patients undergoing 60 endovascular procedures, including aortoiliac, infra-inguinal, and bypass graft lesions. Of these procedures, completely noninvasive evaluation was accomplished in 43 procedures (73%), either by means of duplex scanning ($n=11$, 18%) or by means of MRA ($n=32$, 53%) [120]. The findings at noninvasive examination were confirmed at intraoperative angiography and no additional lesions were identified. ABI and mean limb status category both showed significant improvement. The noninvasive approach was less expensive compared with preprocedural contrast angiography, with $551 saved for each duplex scanning case and $235 saved for each MRA case (not including the $144 cost of postprocedure short-stay unit time required for diagnostic arteriogram).

Angiography Summary

Multiple modalities are now available for angiographic imaging of the lower extremity in the diabetic patient. Catheter angiography, now primarily performed using DSA, is considered the gold standard, because it provides the highest potential spatial resolution, including, in particular, spatial detail in the smaller crural and pedal vessels. Catheter angiography carries risks associated with an invasive technique, but provides the opportunity to combine the diagnostic study with definitive treatment of certain kinds of arterial stenoses. MRA, CTA, and duplex Doppler ultrasound provide noninvasive alternatives for angiographic imaging and continue to improve their capacity to image subtle disease and small vessels. All types of angiographic imaging are reliant on achieving optimal technique in generating and postprocessing of images, in order to attain the highest level of diagnostic accuracy. While the MR contrast, gadolinium, has traditionally been favored over iodinated contrast agents for its low rate of allergic reaction and low incidence of nephrotoxicity, new concerns about the association of NSF with the use of certain gadolinium contrast agents in patients with renal insufficiency have limited its use in patients with renal failure.

Osteomyelitis Versus Neuroarthropathy

Differentiation between osteomyelitis and neuroarthropathy is often difficult. Certain neuroarthropathic changes resemble osteomyelitis. In order to better understand the similarities and differences, imaging characteristics of neuroarthropathy will be presented here. A more complete discussion of neuro-osteoarthopathic changes is provided in another chapter of this book.

Neuroarthropathy

Loss of both pain and proprioceptive sensation is believed to predispose to repetitive trauma, leading to diabetic neuroarthropathy [15]. Though potentially devastating, the incidence of neuropathic joints in the diabetic is surprisingly low, reported to be 0.1–0.5%. The joints of the forefoot and midfoot are commonly involved. The distribution of neuroarthropathy in diabetic patients is 24% in the inter-tarsal region, 30% in the tarsometatarsal region (Fig. 6.21), and 30% in the metatarsophalangeal joints. Abnormalities of the ankle (11%) and interphalangeal (4%) joints are less frequent [121].

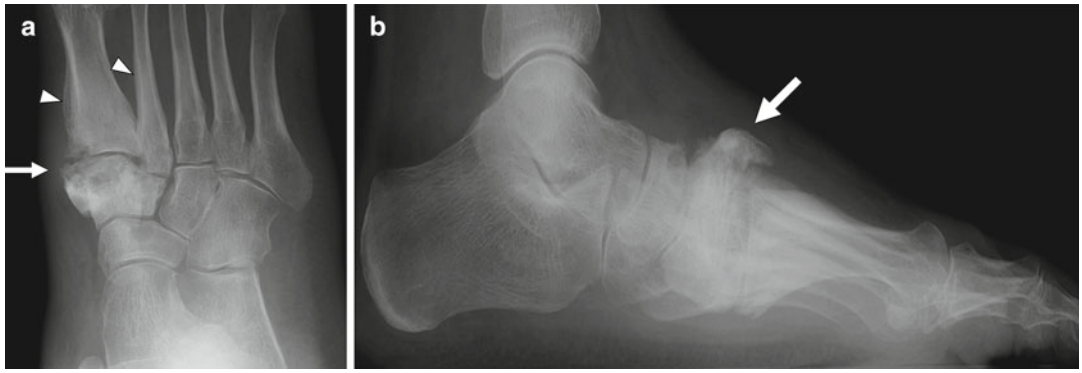

Fig. 6.21 Hypertrophic form of neuroarthropathy. (**a**) AP and (**b**) lateral radiographs show hypertrophic changes in the medial midfoot (*arrows*), centered about the tarsometatarsal joint. There is bony proliferative change, increased density and nonaggressive periosteal new bone formation (*arrowheads*) in the first and second metatarsal bones, and increased density in the corresponding cuneiforms. In its early phase, this form of neuroarthropathy may be confused with osteoarthritis. Note soft tissue swelling, with effacement of fat planes

Two classic forms of neuroarthropathy, atrophic and hypertrophic, have been described [122]. The atrophic form, representing the acute resorptive or hyperemic phase, is characterized by osseous resorption and osteopenia. This form frequently appears in the forefoot and the metatarsophalangeal joints, leading to partial or complete disappearance of the metatarsal heads and proximal phalanges. Osteolytic changes produce tapering or "pencil-pointing" of phalangeal and metatarsal shafts. Marrow changes in the atrophic or hyperemic form show hypointense T1 and hyperintense STIR and mimic the changes seen in osteomyelitis. The hypertrophic form, representing the healing or reparative phase, is characterized by sclerosis, osteophytosis, and radiographic appearance of extreme degenerative change (Fig. 6.21). In its early phase, the hypertrophic form of neuroarthropathy may be confused with osteoarthritis. Concurrent osseous fragmentation, subluxation, or dislocation predominates in the inter-tarsal and tarsometatarsal joints. Ruptured ligaments in the mid- and forefoot cause dorso-lateral displacement of the metatarsal bones in relation to the tarsal bones. This classic finding resembles an acute Lis-Franc fracture-dislocation (Fig. 6.22). Disruption of the talonavicular and calcaneocuboid joints causes collapse of the longitudinal arch, with subsequent plantar displacement of the talus. These changes produce the classic "rocker-bottom" deformity [123]. Recognition of this deformity is important because it creates new pressure points that lead to callus formation and ulceration (Fig. 6.23). Attempts to classify neuropathic joints into the two classic forms may be difficult, as a mixed pattern, composed of both forms, occurs in 40% of neuropathic joints [124].

Osteomyelitis Versus Neuroarthropathy

Other than the characteristic findings of diffuse dark marrow signal on T1-, STIR and T2-weighted MR images associated with hypertrophic neuroarthropathy (versus high T2 and STIR signal seen in osteomyelitis), there is no easy method of distinguishing between osteomyelitis and neuroarthropathy. Secondary findings such as involvement of the midfoot and multiple joints, absence of cortical destruction, presence of small cyst-like lesions, and distance between soft tissue infection and bone changes favor a diagnosis of neuroarthropathy (Table 6.7) [15]. By contrast, osteomyelitis favors the toes or metatarsal heads, and is associated with focal cortical lesions and close proximity to the ulcer.

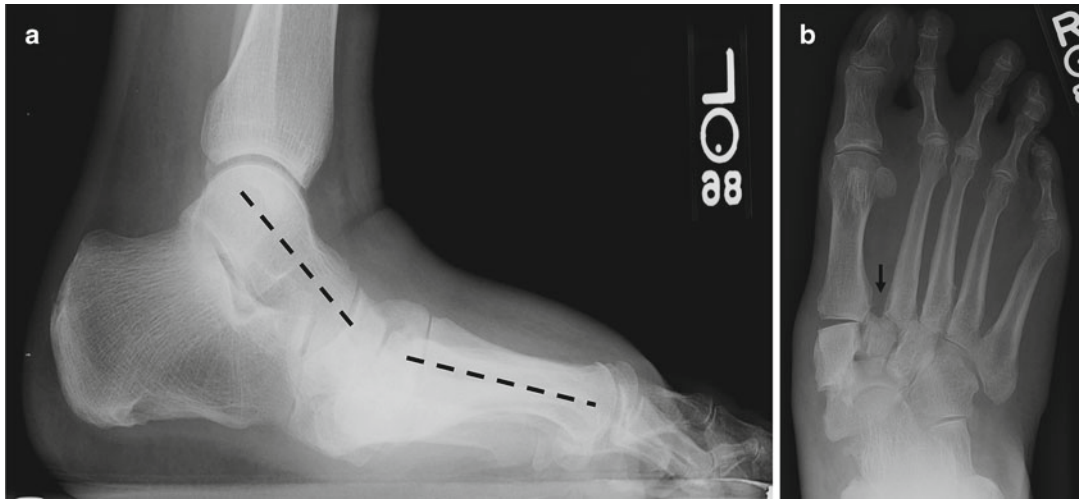

Fig. 6.22 Midfoot deformity related to neuroarthropathy. (**a**) Lateral radiograph demonstrates collapse of the usual longitudinal arch of the foot. Progression can result in extreme "rocker-bottom deformity." (**b**) AP view shows Lis-Franc malalignment (*arrow*) as well as disruption of the navicular-cuneiform articulations

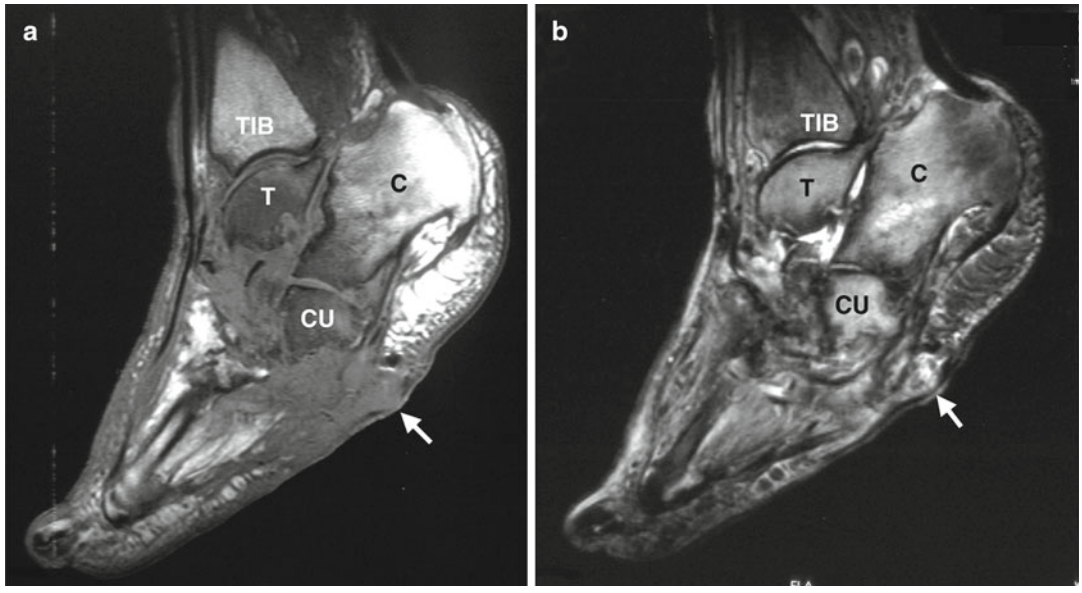

Fig. 6.23 Rocker-bottom deformity and ulceration at focus of high plantar pressure on MRI. (**a**) Sagittal T1-weighted and (**b**) STIR images show disruption of the talonavicular joint causing collapse of the longitudinal arch. These changes produce the classic "rocker-bottom" deformity. This deformity is important because it creates new pressure points that lead to callus and ulcer formation (*arrow*). The diffuse marrow edema associated with neuroarthropathy of the tarsal bones mimics osteomyelitis. *T* talus, *CU* cuboid, *C* calcaneus, *TIB* tibia

Table 6.7 Osteomyelitis versus neuroarthropathy

	Favors osteomyelitis	Favors neuroarthropathy
Radiography		
Location	Forefoot, metatarsal heads, and toes	Mid foot
Cortical destruction	Discrete cortical lesion	Absent
Proximity to soft tissue ulcer	Beneath or close to the ulcer or soft tissue infection	Some distance from soft tissue infection or ulcer
MR		
Signal characteristics of the abnormal marrow	Hyperintense STIR or T2 marrow signal (This signal pattern is nonspecific and overlaps the hyperemic form of neuroarthropathy and acute fracture)	Hypointense marrow signal on all T1, T2, and STIR sequences (This signal pattern corresponds to the hypertrophic form of neuroarthropathy)
Cysts	Not common in osteomyelitis	Well marginated cyst-like lesions, hypointense on T1 and hyperintense on T2

Imaging Algorithm: Approaches to Diagnosis of Pedal Osteomyelitis in the Diabetic Patient

A suggested algorithm for imaging pedal osteomyelitis in the diabetic patient is presented in Fig. 6.24.

Soft Tissue Ulceration Exposing Bone

When the soft tissue ulcer exposes bone, no imaging is needed to confirm the diagnosis of osteomyelitis. Radiography is appropriate to provide a baseline and to document bone complications

Soft Tissue Inflammation (Ulcers and/or Cellulitis) with No Exposed Bone

Radiographic findings are used to further separate the patients into two groups. If the radiographs are normal and the clinical suspicion for osteomyelitis is high, a three phase bone scan can effectively detect or exclude osteomyelitis. MRI or labeled leukocyte study is an acceptable alternative [24]. A gallium scan may replace labeled leukocyte study if the latter is not available [125]. Unlike plain radiographs, these modalities should become positive in the first few days of infection. In light of their high sensitivity, these studies provide a high negative predictive value for osteomyelitis. If the bone scan is equivocal, supplementary imaging with either MRI or labeled leukocyte scans is required.

When the radiographs are abnormal, showing neuroarthropathic, degenerative, or traumatic changes, either labeled leukocyte scan or MRI is acceptable. The choice depends on the location of the suspected osteomyelitis. If the inflammation is in the forefoot, an indium leukocyte study efficiently identifies osteomyelitis. By contrast, when the infection is in the mid- or hindfoot, MRI adequately separates bone from soft tissue inflammation.

Conclusion

Imaging plays an important role in the assessment of the diabetic patient with foot problems. Nuclear medicine and MRI techniques detect osteomyelitis, characterize various soft tissue abnormalities, and depict the extent of bone involvement. Digital subtraction angiography and noninvasive angiographic studies can be used in complementary fashion to evaluate lower extremity arterial anatomy and pathology. Nevertheless, distinguishing osteomyelitis from coincident neuropathic change remains a challenge. Only with an understanding

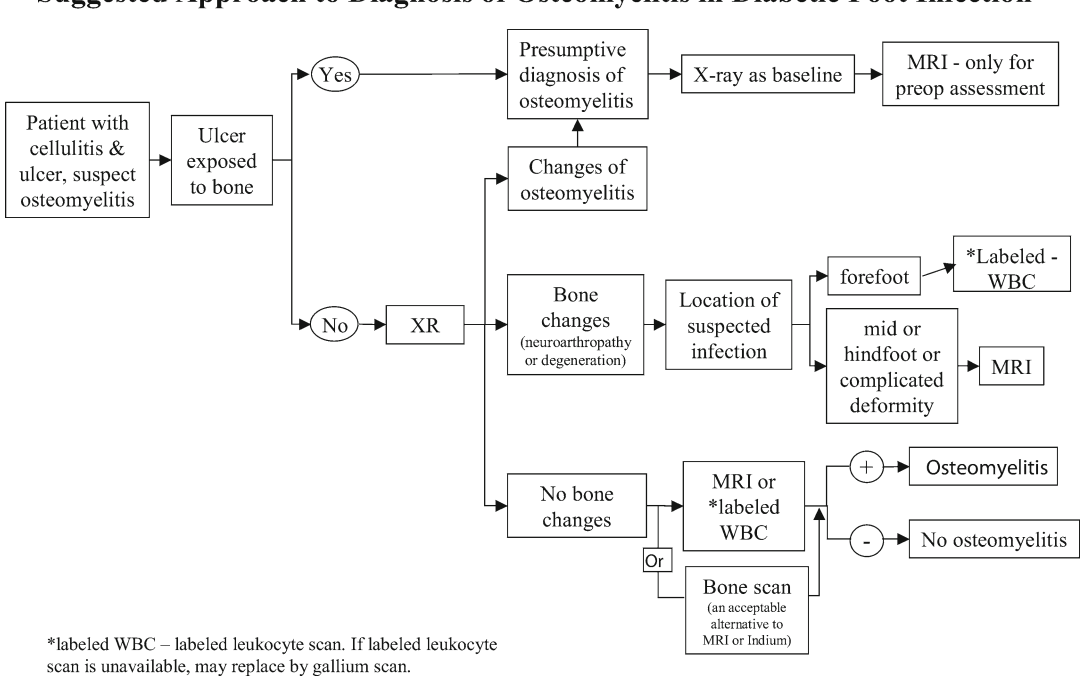

Fig. 6.24 Suggested approach to diagnosis of osteomyelitis in diabetic foot infection. (*Asterisk*) Labeled WBC refers to a labeled leukocyte scan. If labeled leukocyte scan is unavailable, may replace with gallium scan

of the specific strengths and weaknesses of each modality, as they apply to the particular clinical problem in question, can this wide variety of imaging studies be utilized in an effective and efficient manner.

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Part II

Pathophysiology

Physiology and Pathophysiology of Wound Healing in Diabetes

7

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Abstract

Wound healing is an evolutionary conserved process that aims to restore the damaged barrier. This complex process involves many cellular responses including inflammation, proliferation, migration, angiogenesis, and tissue remodeling. Immediately after the injury, blood components are released into the wound site, activating the clotting cascade. The resulting clot induces hemostasis and provides a matrix for the influx of inflammatory cells. Inflammation is characterized by leukocyte migration and arrival to the site of injury. Neutrophils arrive first to remove contaminating bacteria (Singer and Clark, N Engl J Med 341(10):738–746, 1999) and are followed by monocytes, which differentiate into macrophages. Macrophages play an important role in augmenting the inflammatory response and tissue debridement. At the same time, many different cell types respond to initial inflammatory signals and start migrating to the wound site, including keratinocytes, endothelial cells, and circulating and local progenitor cells.

Keywords

Clotting cascade • Hemostasis • Cellular responses • Keratinocytes • Fibroblasts • Endothelial cells • Neutrophils • Macrophages • Stem and progenitor cells • Angiogenesis • Wound healing

Physiology of Wound Healing

Wound healing is an evolutionary conserved process that aims to restore the damaged barrier. This complex process involves many cellular responses including inflammation, proliferation, migration, angiogenesis, and tissue remodeling. Immediately after the injury, blood components

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are released into the wound site, activating the clotting cascade. The resulting clot induces hemostasis and provides a matrix for the influx of inflammatory cells. Inflammation is characterized by leukocyte migration and arrival to the site of injury. Neutrophils arrive the first to remove contaminating bacteria [1] and are followed by monocytes, which differentiate into macrophages. Macrophages play an important role in augmenting the inflammatory response and tissue debridement. At the same time, many different cell types respond to initial inflammatory signals and start migrating to the wound site, including keratinocytes, endothelial cells (ECs), and circulating and local progenitor cells. Once they arrive they start to proliferate. Proliferation is characterized by re-epithelialization, neovascularization, and granulation tissue formation. Granulation tissue formation begins during the inflammation phase, forming a "beefy red" and highly vascular region of the healing tissue, predominantly relying on neovascularization [1]. During this phase, the immature fibrin matrix and granulation tissue are replaced by collagen and scar. Wound healing as a process does not end by wound closure, although this is the visible sign of complete healing. Upon closure, tissue is continuing with collagen deposition and cross-linking. During this remodeling phase, balance is established between collagen synthesis and destruction, whereby the scar gains its tensile strength [2]. Wound healing in adults results with a scar formation, fibrosis, and contracture. However, fetal skin, up to midway to the last trimester, heals without scar formation, using a regenerative pathway [3].

Cellular responses to injury involve direct cell–cell and cell–matrix interactions, as well as the indirect cross talk between different cell populations by soluble mediators. Thus, wound healing is orchestrated through the integration of multiple signals (growth factors, cytokines, and chemokines) released by participating cells: keratinocytes, fibroblasts, endothelial cells, macrophages, and platelets. The appropriate balance of these signaling factors as well as their spatio-temporal control is essential for successful wound healing [4–6]. Below we discuss in more detail functions of various contributing cells: keratinocytes, fibroblasts, endothelial cells, neutrophils, macrophages, and progenitor cells.

Cellular Components of Wound Healing

Keratinocytes

Keratinocytes play several critical roles in the wound healing process and are among the most important cells that respond to injury and accelerate healing. Under normal conditions, keratinocytes main role is barrier formation of the skin. During wound healing, keratinocytes play many important roles, including the release of cytokines and growth factors, which recruit other cell types and stimulate matrix formation and angiogenesis, respectively. Keratinocytes also migrate and proliferate within the wound bed to accelerate closure in a timely fashion.

In healthy skin, keratinocytes proliferate in the basal cell layer and differentiate in the suprabasal layers. Basal keratinocytes are mitotically active and help form the basement membrane by advancing cross talk with dermal fibroblasts, melanocytes, and Langerhans cells. When keratinocytes leave the basal cell layer, they change phenotypically and begin the process of differentiation. During this process, keratinocytes stop dividing, change their keratin production from K5/K14 to K1/K10, and begin producing a number of insoluble proteins. Terminal differentiation results in loss of nuclei and protein cross-linking, giving rise to a cornified layer and forming an epidermal barrier [7, 8]. This perpetual process of keratinocyte differentiation governs the maintenance of barrier.

Keratinocytes are responsible for barrier maintenance and they are equipped for rapid response to its damage. When the epidermal barrier is disrupted upon skin injury, keratinocytes release prestored interleukin-1 (IL-1), alerting surrounding cells to barrier damage [9, 10]. The signals released by keratinocytes act in both auto- and paracrine manners. This process, termed the "keratinocyte activation cycle," is characterized by changes in cellular behavior (migration and proliferation), induced secretion of a multitude of growth factors and cytokines and expression of

K6, K16, and K17 keratin proteins, which are often considered one of the first markers of epidermal healing [11, 12].

To close the gap in the epidermal barrier, keratinocytes at the wound edge first loosen their adhesion to each other and to the basal lamina. In addition, keratinocytes obtain the flexibility and ability to migrate over the extracellular matrix (ECM) deposited by dermal fibroblasts. This process requires rearrangement of integrin receptors and reassembly of the associated actin cytoskeleton and the keratin filament network [8]. Further, epidermal growth factor (EGF), keratinocyte growth factor (KGF), transforming growth factor alpha (TGF-α), fibroblast growth factor (FGF), IL-1, and Interleukin-6 (IL-6) have been shown to be among the important regulators of keratinocyte proliferation, migration, and re-epithelialization and communication with other cell types [5, 9].

Upon the advancement of the migrating epithelial tongue and first layer covering the wound, keratinocytes also start to proliferate to ensure an adequate supply of cells to encase the wound. Once the wound is healed, defined as being fully epithelialized with no drainage, and covered by a keratinocyte monolayer, the proliferation signals cease and a new stratification process begins. Thus, keratinocytes become "deactivated" and revert to their previous normal differentiation patterns.

Fibroblasts

Complex interactions and cross talk between fibroblasts, keratinocytes, and other cell types participating in wound healing is critical for successful wound closure. Fibroblasts play a vital role in wound healing as they migrate, proliferate, and supply an ECM during tissue repair. Under normal conditions, fibroblasts synthesize collagen and ECM, maintaining the structural integrity of the skin. Much like keratinocytes, fibroblasts' various roles are tightly regulated by cytokine and growth factor signaling over the course of wound healing. One of the many important roles of fibroblasts is to provide contractile properties to the wound as myofibroblasts. As an early response to wounding, dermal fibroblasts at the site of injury begin to proliferate. A few days upon wounding, fibroblasts begin migration into the provisional matrix of the wound clot to lay down their own collagen-rich matrix [13]. This ECM acts as a "scaffold" during tissue repair, providing structural support and attachment sites for cell surface receptors and it also works as a regulated "reservoir" for signaling molecules that modulate diverse processes such as angiogenesis, cell proliferation and migration, and inflammation [14]. In order to migrate into the clot, dermal fibroblasts must downregulate their collagen receptors and upregulate integrins that bind ECM proteins such as fibrin, fibronectin, and vitronectin [15]. During their migration, fibroblasts sense signals coming from both their matrix environment and from the growth factor milieu that surrounds them.

About 1 week after wounding, the wound clot will be fully invaded by activated fibroblasts. These fibroblasts are stimulated by TGF-β1 and other growth factors to synthesize and remodel a new collagen-rich matrix [13]. At the same time, a proportion of the wound fibroblasts transforms into myofibroblasts, which express α-smooth muscle actin and resemble smooth muscle cells in their capacity for generating strong contractile forces [16].

Conversion from fibroblasts to myofibroblasts is triggered not only by growth factors such as TGF-β1 [16] but also by mechanical tension [17, 18]. The appearance of myofibroblasts coincides with a strong induction of contractile properties so that cells align parallel to mechanical tension that is building up in the granulation tissue. The various tensile forces acting on and exerted by wound fibroblasts before, during, and after contraction have been studied in collagen-gel models. A number of growth factors at the wound site are potent stimulators of fibroblast-driven gel contraction and presumably signal granulation tissue contraction in vivo [19]. Platelet-derived growth factor (PDGF)-AA and -BB isoforms and TGF-β1 led to efficient collagen-gel contraction [19–21]. IL-1α was shown to cause degradation of the collagen gels at later time points, most likely due to enhanced matrix metalloproteinase (MMP) activity [22].

Contraction stop signals are also being analyzed by releasing mechanically stressed anchored gels from their substrate attachments to simulate the loss of resistance after a wound has closed. Within minutes of release from resisting forces, PDGF and EGF receptors on the cell surface become deactivated [23] and the relaxed cells return to a quiescent state similar to that existing before the injury. Programmed cell death also occurs in the granulation tissue fibroblasts, triggered by TGF-β1 and FGF at the injury site, after wound contraction has ceased [24, 25].

Given the importance of fibroblasts and keratinocytes in proper wound healing, human skin substitutes have been developed as a wound treatment modality. Currently, a living skin equivalent, composed of living fibroblasts and keratinocytes in a native collagen matrix, is the only FDA-approved skin substitute [26]. Please see section on "Treatment for DFUs" for additional information.

Endothelial Cells

Additional responders to wound healing signals released by fibroblasts and keratinocytes are local endothelial cells. ECs are normally positioned within the vascular lumen and form the tubular structure of blood vessels. ECs act as a barrier between intraluminal blood and extravascular tissue. During angiogenesis, growth factors, cytokines, and cell–cell and cell–matrix interactions activate ECs. Activated ECs, platelets, macrophages, and fibroblasts release proangiogenic cytokines, leading to the invasion and migration of ECs into the ECM, EC proliferation, and new immature vascular formation [27].

Before ECs can begin angiogenesis, they must disrupt their interactions with neighboring ECs, digest the basement membrane and components of the ECM [27, 28]. Proteolytic enzymes, including serine proteases, urokinase plasminogen activator, and MMPs, are released by ECs to digest the basement membrane and ECM [29]. Once this is achieved, ECs are allowed to migrate to the site of new vessel formation [27]. MMPs digest the basement membrane and the ECM, ultimately allowing ECs to migrate and proliferate [29]. In a recent study, the addition of MMP synthetic inhibitor to EC cultures significantly decreased angiogenic activity [29]. ECs migrate to the site of new vessel formation by chemotaxis [27]. Further, specific adhesion molecules, integrins, mediate their cell–matrix interactions to ensure migration to the site of new vessel formation [27]. Integrins are adhesion molecules that are highly upregulated on ECs undergoing angiogenesis [30, 31].

Neutrophils

Inflammation in normal wound healing is essential, but must be tightly regulated both temporally and spatially by a variety of cell types. Immediately after injury extravagated blood constituents form a haemostatic plug. Platelets and polymorphonuclear leukocytes (also known as neutrophils or PMNs) entrapped and aggregated in the blood clot release a wide variety of factors that amplify the aggregation response, initiate a coagulation cascade, and/or act as chemoattractants for cells involved in the inflammatory phase [32]. At the same time, rapid activation of resident skin immune cells (mast cells, γδ T cells, and Langerhans cells) occurs [33–35]. The inflammatory phase continues with active recruitment of neutrophils and then macrophages from blood vessels, which is orchestrated by growth factor signals from the resident cells, mainly keratinocytes, and by foreign epitopes such as the lipopolysaccharides (LPS) of invading microorganisms [36]. Neutrophils arrive at the wound site within minutes of wounding and become the predominant cells in the wound for the first 2 days after the injury occurs, with especially high numbers on the second day. Extravasation of PMNs from blood vessels is activated by proinflammatory cytokines IL-1β, TNF-α, and IFNγ at the wound site, leading to expression of various classes of adhesion molecules essential for cell adhesion and diapedesis. Adhesion molecules crucial for neutrophil diapedesis include endothelial P- and E-selectins as well as ICAM-1, -2 [36]. PMNs have an important bactericidal role and kill invading microorganisms through several strategies, including bursts of reactive oxygen species (ROS) [32]. Inflammatory cells also exert their influence on the surrounding tissue by generating

nitric oxide (NO) and large amounts of ROS [37]. Chemokines are also very important mediators of neutrophil recruitment during tissue repair [38–40]. Gene expression profiles of wound PMNs suggested that these cells influence many other aspects of repair, such as resolution of the fibrin clot and provisional ECM, promotion of angiogenesis, and re-epithelialization [41]. The neutrophil infiltration ceases after a few days, and expended neutrophils are themselves phagocytosed by macrophages, which are present at the wound site within 2 days after injury.

Macrophages

Release of signals from keratinocytes and fibroblasts leads to recruitment of both local resident macrophages and those from the blood. Monocytes are drawn from the circulation somewhat later than neutrophils and their numbers peak a day or so after injury [36]. Once they leave the circulation, monocytes mature into macrophages and change their expression profiles and behavior according to the surroundings and growth factor stimuli [42]. At the wound site, they clear up matrix and cell debris, including spent neutrophils by phagocytosis [36].

Macrophage infiltration into the wound site is regulated by different chemotactic factors, including growth factors, proinflammatory cytokines, and chemokines (macrophage inflammatory protein 1α, MCP-1, RANTES) [4, 43–45]. Major sources of these chemoattractants at the wound site include platelets trapped in the fibrin clot at the wound surface, keratinocytes at the wound edge, fibroblasts, and leukocytes subsets. Both types of macrophages, classically activated (M1, proinflammatory) and alternatively activated (M2, anti-inflammatory and proangiogenic), are present in early phases of inflammation, but M2 macrophages predominate later in repair [46, 47]. In addition to their immunological functions as antigen-presenting cells and phagocytes during wound repair, macrophages also release a battery of growth factors and cytokines at the wound site, which further promotes cell proliferation and the synthesis of ECM molecules by resident skin cells [46, 47].

Inflammatory cells also exert their influence on the surrounding tissue by generating nitric oxide (NO) and large amounts of ROS [37]. NO and ROS are known to drive certain aspects of repair [48] but at the same time affected wound cells must protect themselves by detoxifying programs [37]. NO is a very transitory molecule, whose levels together with inducible NO synthase (iNOS) activity shows a distinct time course during normal healing [49, 50]. Although the issue of whether inflammatory cells are an essential requirement for repair remains controversial [51], it is clear that these cell populations exert a profound influence on all other cells within the wound and in the surrounding tissue. One of the important roles of inflammatory cytokines is to regulate angiogenesis, which they accomplish in concert with signals from other wound cells and from serum (see section on “Angiogenesis”). However, nonhealing wounds fail to progress through the normal phases of wound repair, but instead remain in a chronic inflammatory state. Imbalances in wound proteases and their inhibitors in chronic wounds, because of sustained production of inflammatory mediators and influx of inflammatory cells, prevent matrix synthesis and remodeling, essential for progression to a healed wound [52–56].

The inflammatory phase of wound healing has been studied in detail, but most of the research efforts were focused on the onset of inflammation and little is known about inflammation resolution. Better understanding of how inflammation resolves will provide a basis for novel treatment modalities favoring the closure of chronic wounds.

Stem and Progenitor Cells in Wound Healing

In order to have sustained healing without scarring, Fu et al. suggested combining growth factors with stem cell therapy so that sweat glands, sebaceous glands, and hair follicles could be reconstituted with a more functional integument [6]. Therefore, stem and progenitor cells are of great interest to wound healing as active participants as well as potential therapeutic approach.

The ability of the skin to replenish itself and contribute to the maintenance of tissue renewal

and homeostasis relies on resident populations of stem cells (SCs) [57–59]. To date, SCs of the skin have been identified to occupy at least three distinct niches: the bulge of the hair follicle, the base of the sebaceous gland, and the basal layer of the epidermis [59–64]. Whereas the SCs of the sebaceous gland niche and the interfollicular basal layer niche have only been proven to behave unipotently exclusively maintaining homeostasis of their respective tissue, the SCs of the hair bulge have been long thought to maintain a multipotent nature: serving as a reservoir for renewal of not only hair but also sebaceous glands in conditions of hyperproliferation and interfollicular epidermis subsequent to wounding [65]. This is not surprising as it is known that the basal layer and the hair follicle outer root sheath are not only connected but also biochemically similar [66]. If stimulated adequately epidermal SCs have even the potential to develop additional cell types and tissues [67–70]. In the healthy skin, SCs are quiescent [71]. However, in response to injury, SCs niches lose their quiescence and resident SCs are recruited to replace the damaged tissue [72–74]. SCs of the hair bulge are required for regenerating the interfollicular epidermis in response to wounding [75] and the most recent studies have shown major contribution of hair follicle in anagen phase during tissue repair [76]. Importantly, in addition to the hair follicle bulge SCs, recent studies discovered other populations of epithelial SCs within distinct regions of the hair follicle [77]. Although epidermal SCs have been characterized largely by their functional properties and marker expression [78, 79], their full therapeutic capacity is still elusive.

Amnion-derived multipotent progenitor cells (AMP cells) provide another avenue for therapeutic approach to wound healing as well as diabetic foot ulcers (DFUs). AMP cells display many favorable characteristics of stem cells, including the ability to differentiate to many cell types such as skin, hair, neurons, cardiac muscle, liver, pancreas, and possibly vascular tissue [80, 81]. They are isolated from the full-term placenta, which makes them abundantly available. From a safety standpoint, the low antigenicity of amnion [82] and documented nontumorigenicity [81] is an advantage for use as a cell replacement therapy. Amniotic membrane and human amniotic epithelial cells are used on skin wounds, burn injuries, and chronic leg ulcers and to prevent adhesions in surgical procedures [83–91]. Amniotic membrane is also used in ocular surface reconstruction to promote development of normal corneal or conjunctival epithelium [92]. Human amniotic membrane and hAEC have been shown to survive for prolonged times in immunocompetent animals, including rabbits [92], rats [93], guinea pigs [94], and bonnet monkeys [95]. In addition, long-term engraftment was observed after i.v. injection of heterogeneous human amniochorionic cells into newborn swine and rats, with human microchimerism detected in bone marrow, brain, lung, and thymus [96], suggesting active migration and integration into specific organs and indicating active tolerance of the xenogeneic cells. Amnion-derived cells have been shown to secrete many cytokines that are associated with wound healing and some have been credited with contributing to scarless healing in the fetus [97–107].

These therapies have also been important in demonstrating that local therapy is clinically effective in the treatment of DFUs and will be useful approach to implement findings from this project into future treatments. Adult bone marrow (BM) is well known source of multipotent adult progenitor cells that can differentiate into many adult tissue types in vivo and in vitro when placed in the proper cytokine environment [108, 109] and may provide a alternative for progenitor cell therapy approach. Multipotent adult progenitor cells could also home to injured tissues and participate in the repair and regeneration [110, 111]. It has been known that bone marrow (BM) provides inflammatory cells and endothelial progenitor cells (EPCs) during normal wound healing. However, recent studies strongly suggest that the BM contributes not only to inflammation and angiogenesis, but also to keratinocytes and fibroblast-like cells [112–114]. Most importantly, wounding can stimulate the engraftment of bone marrow-derived mesenchymal stem cells (BM-MSCs) to the skin promoting wound healing [115].

BM-MSCs are self-renewing SCs characterized by specific markers—CD105, CD73, and CD9 [116]. They represent about 0.001–0.01% of the nucleated BM cells, but the fact that they are expandable in culture and capable of differentiating into several cell types [117] makes them very attractive for therapeutic purposes. A number of animal studies have shown that BM-MSCs contribute to the repair/regeneration of a variety of injured tissues including the myocardium [118, 119], bone and cartilage [120], tendon [121], and most importantly skin [121, 122]. Moreover, topically applied autologous BM-MSCs have shown potential to heal human chronic wounds that are recalcitrant to other treatments [123, 124]. Many other mesenchymal tissues also contain committed lineage-directed mesenchymal precursor cells, which participate in local regeneration. MSCs from the skin and other tissues, like adipose tissue, muscles, and scalp tissue resemble BM-MSCs and express similar markers [125–127]. Skin fibroblasts are also a useful source of cells from which pluripotent SCs may be generated [128]. Another type of circulating bone marrow-derived progenitor cells, called fibrocytes, have been suggested to migrate into the wound and contribute to the formation of the myofibroblastic population of granulation tissue [129]. Fibrocytes participate in tissue remodeling by producing ECM proteins (i.e., collagen I and collagen III) and by secreting MMPs [130].

Bone marrow-derived EPCs are the essential cells for vasculogenesis [131]. Vasculogenesis likely begins when BM multipotent progenitor cells differentiate into early EPCs [109, 132], at which time the cells acquire hematopoietic endothelial lineage specific cell surface markers [133, 134]. EPCs are undifferentiated in the BM and in a quiescent state in two zones [27]. One zone, the osteoblastic zone, maintains EPCs in the GO phase of the cell cycle and keeps the EPCs in close proximity with stromal cells [132, 135]. The second zone, the vascular zone, maintains EPCs in the S phase or G2/M phase of the cell cycle, which is readily available to differentiate into tissue-specific progenitor cells and enter the peripheral circulation [132]. EPC mobilization from the BM into the circulation is thought to occur via cytokine-mediated pathways [133]. These cytokines include the vascular endothelial growth factor (VEGF) family and stromal-cell-derived factor-1 (SDF1α) [133]. Early EPCs that exit the bone marrow are positive for CD133, CD34, and VEGF-R2, which are specific to EPCs determined to become endothelial cells. Next, EPCs enter the peripheral circulation and migrate to areas of vasculogenesis. In the circulation, the early EPCs differentiate into late EPCs by losing CD133 and gaining other, more specific EC surface markers [136]. In the circulation, EPCs constitute 0.002% of mononuclear cell fraction of whole blood [137]. This pool of circulating EPCs is increased when vasculogenic stimuli are released for neovascularization. EPCs play an important role in normal wound healing [138–140]. Multiple studies have shown that EPCs derived from diabetic mice exhibited impaired vascularization and wound healing which could be reversed by ischemia-induced upregulation of SDF-1α [2, 138]. Consistent with the effect of EPCs on wound healing in animal models, impaired function and reduced numbers of circulating EPCs have been described in both type 1 and type 2 diabetic patients [141, 142], suggesting that modulation of EPC numbers and function has a potential for therapy for DFUs.

In summary, there is a profound therapeutic potential of progenitor cells and a great interest in current developments of stem or progenitor cells therapy for treatment of wound healing disorders, including DFUs.

Pathophysiology of Wound Healing in Diabetes Mellitus

Over 170 million patients worldwide are affected by diabetes, with an estimated 20.8 million affected in the USA [143]. By 2030, these numbers are projected to double [144]. DFUs occur in 15% of patients with diabetes and are a leading cause of hospital admissions for people with diabetes in the developed world [145, 146]. DFUs precede 84% of all diabetes-related leg amputations [146] and lead to pain, suffering, and poor quality of life [2].

As mentioned earlier, wound healing is a dynamic process involving overlapping inflammatory, proliferating, and remodeling phases. It engages the coordinated action of both resident and migratory cell populations within the ECM environment. However, in individuals suffering from DM, wounds fail to heal in a timely and orderly manner. The pathophysiologic relationship between diabetes and impaired healing is multifactorial. Vascular, neuropathic, immune functions and biochemical abnormalities each contribute to the altered tissue repair in diabetic patients.

Extrinsic factors such as callus formation, excessive pressure, and wound infection also play a role in healing impairment. In addition, lack of glucose control impairs local leukocyte defenses and persisting hyperglycemia contributes to the metabolic pathophysiology of diabetes-related complications.

From the extensive research conducted so far, it appears that diabetes negatively affects majority of cellular processes in wound healing. Studies show that prolonged inflammatory phase in diabetic wounds causes delay in the formation of mature granulation tissue and subsequently reduction in wound tensile strength [147]. Diabetic wounds show decreased number and function of neutrophils and macrophages. Macrophage efferocytosis is dysfunctional (e.g., efficient dead cell clearance at the wound site), thus resulting in increased apoptotic cell burden and higher expression of proinflammatory and lower expression of anti-inflammatory cytokines [148–150]. For example, increased levels of tumor necrosis factor alpha (TNF-α) found in diabetic wounds may lead to decreased fibroblast proliferation and increased apoptosis by inducing caspase activity [150]. On the other hand, sustained inflammatory response and deregulated expression of cytokines may amplify caspase activity as well [151, 152].

Fibroblasts from diabetic wounds look different than healthy fibroblasts. They are usually large and inflated compared to the spindle-shaped morphology of the fibroblasts in age-matched controls. Fibroblasts from diabetic wounds show numerous vesicular bodies, dilated endoplasmic reticulums, and lack of microtubular structure [153]. In addition to a reduced number and morphological changes, fibroblasts from diabetic wounds exhibit diminished proliferative capacity that contributes to a decreased production of ECM proteins, delayed wound contraction, and impaired wound healing [153, 154]. On the contrary, activity of some MMPs is found increased in diabetic wounds when compared to acute wound healing [155]. Increased expression of MMP8 and MMP26 was found in tissue from DFUs [156]. MMP2 and MMP9 show sustained overexpression in chronic nonhealing DFUs [157]. The latest report implicates MMP9 levels in wound fluid as a predictor of poor wound healing in DFUs [158]. The ratio of MMP and tissue inhibitor of metalloproteinases (TIMP), which in normal physiological conditions maintains the proteolytic balance, is found to be disturbed in DFUs. High MMP1/TIMP1 ratio has been shown as a predictor of wound healing in DFUs [159]. In contrast, high MMP9/TIMP1 ratio predicts poor wound healing [158] (Table 7.1). The combination of increased concentrations of MMP2, MMP9, MMP14 with decreased concentrations of TIMP2 in DFUs suggests that the increased proteolytic environment significantly reduces the formation of new connective tissue matrix and contributes to the failure of diabetic wounds to heal. Overall, these changes lead to decreased tensile strength in diabetic wounds [152, 160].

The decrease in growth factors responsible for tissue repair such as TGF-β may explain deregulation of MMPs [161]. It is known that most MMP genes have TGF-β inhibitory element in their promoter regions and thus a possible explanation for deregulation of MMPs is that reduced levels of TGF-β lower down the inhibitory regulatory effect on MMP genes and cause overexpression of MMPs [162, 163]. However, the exact mechanism responsible for increased MMP activity in diabetes is still to be elucidated. The lack of TGF-β signaling in chronic wounds could also lead to the increased iNOS activity and greater NO synthesis [164], since TGF-β1 has been demonstrated to downregulate iNOS activity in macrophages and epithelial cells [165, 166]. Although NO can stimulate angiogenesis, excessive amounts may have an inhibitory

Table 7.1 Deregulated matrix metalloproteinase (MMPs) and their inhibitors (TIMPs) in DFUs

↑	MMP2
↑	MMP8
↑	MMP9
↑	MMP14
↑	MMP26
↓	TIMP1
↓	TIMP2
↑	MMP1/TIMP1 Predictor of healing ulcers
↑	MMP9/TIMP1 Predictor of poor healing

effect by decreasing endothelial cell and lymphocyte proliferation, and possibly inhibiting platelet and leukocyte activation [167–169]. In patients with diabetes, elevated levels of plasma NO have found to be associated with recurrent ulcers [170]. In addition to lower concentrations of growth factors, diabetic wounds contain fibroblasts that show diminished response to growth factors such as EGF, IGF-I, bFGF, PDGF-AB, GM-CSF, and VEGF [153, 166, 171–173]. We have shown that fibroblasts cultured from the different wound locations (e.g., nonhealing edge, wound base, and adjacent skin) show differences in the response to the various growth factors [154].

Similar to fibroblasts, epidermal keratinocytes display dysfunction in DFUs. One study found that epidermal keratinocytes at the edge of DFUs express pathogenic markers beta-catenin, and c-myc and show abnormal localization of EGF receptor (Fig. 7.1). Keratinocytes appear to be trapped between proliferation and differentiation. Epidermis comprising nonhealing edges of DFUs is acanthotic, hyper-, and para-keratotic [174, 175]. Hyperproliferative keratinocytes show an activated phenotype and are negative when stained for keratins involved in epidermal differentiation. In addition to deregulated proliferation and differentiation, there is a reduced expression of a key molecule present on migrating epithelium LM-3A32 (uncleaved, precursor of the α3 chain of laminin 5) contributes to impaired migratory capacity of these cells [176, 177]. Over expression of EGF, GM-CSF, and TGF-β1 in DFU

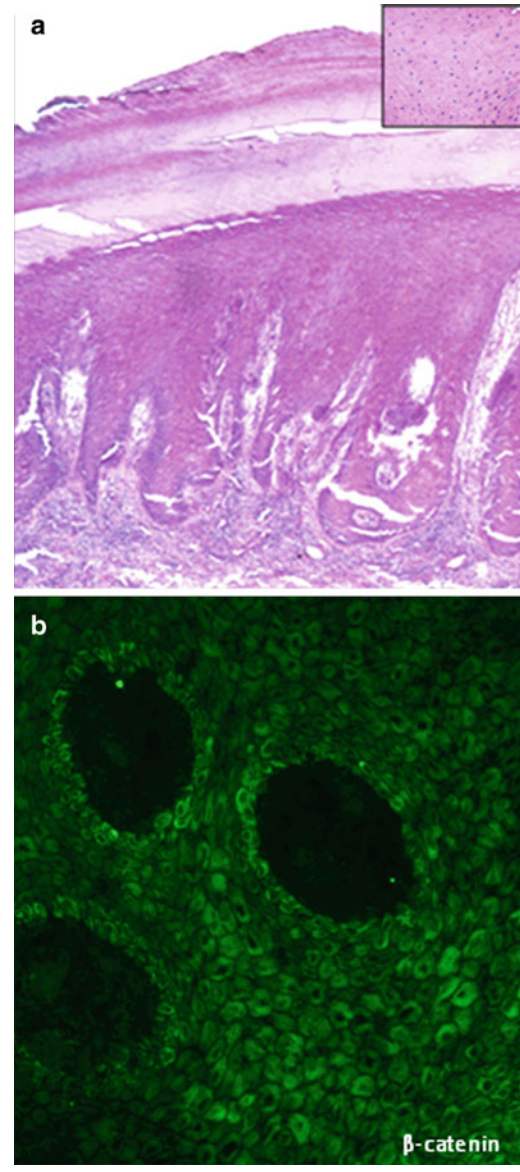

Fig. 7.1 A typical nonhealing edge of a DFU shows hyperproliferative epidermis with nuclei present in cornified layer (*inset*) (**a**). Immunofluorescence with a beta-catenin specific antibody. Beta-catenin is present in the nuclei of a nonhealing DFU epidermis (**b**)

epidermis is also postulated to play a role in deregulated keratinocyte proliferation, lack of keratinocyte apoptosis, and migration in these ulcers [161]. Tissue from DFUs show accumulation of CD1a+ Langerhans cells (LC) in epidermis compared to normal skin and insufficient upregulation of beta-defensin-2 (hBD2) [178].

Many other factors such as decrease in heat shock protein expression, decreased chemotaxis, less antioxidant synthesis, and increased oxygen free radical generation have been shown to play a role in pathogenesis of diabetic healing [179].

The local environment of the diabetic wound is healing impaired due to high bacterial burden and the barrier to diffusion of growth factors and cytokines important for healing. In addition, prolonged hypoxia correlates with healing inability [139]. Hypoxia is pathologically increased in diabetic wound healing [139]. Oxygen tension is positively correlated with collagen production [180–182] and bacterial killing [183, 184].

Diabetics are at an increased risk for infection due to high bacterial burden. It has been reported that diabetic patients have a 25% chance of developing a DFU and a greater than 50% chance of these ulcers becoming infected [185, 186]. Further, diabetic patients have a tenfold increased chance of being hospitalized with a bone or soft tissue infection than those without diabetes [185–187]. Infection and subsequent biofilm production undermines healing in DFUs. Biofilms are polymicrobial populations of cells encased in hydrated extracellular polymeric substances and attached to a surface (e.g., tissue) [188] It has been proven that one of the greatest barriers to healing in chronic wounds is biofilm due to polymicrobial infections [189–191]. Furthermore, it has been shown that biofilms are more prevalent in chronic, nonhealing wounds, and rare in acute, healing wounds [192].

One of the most significant risk factors for the development of DFUs is diabetic neuropathy leading to amputations, infections, morbidity, and mortality. The prevalence of diabetic neuropathy ranges from 7% within 1 year of diagnosis to 50% for those with diabetes for >25 years [193]. Thus, as patients age, diabetic neuropathy prevalence increases; it is present to some degree in >50% of patients over 60 years [145, 194]. Diabetic neuropathy increases the risk of foot ulceration by sevenfold [195]. Diabetic neuropathy predisposes the diabetic foot to various complications including ulceration [195] and disabling joint deformity [196]. One of the ways diabetic neuropathy causes damage is via altered autonomic regulation of cutaneous blood flow [197]. Further, motor neuropathy leads to atrophic changes in the foot musculature, leading to foot deformity and decreased joint mobility [196]. Ultimately, these complications further the risk for DFU. Therefore, identifying at-risk diabetic patients is crucial for the prevention of foot ulceration and various screening methods are used for this, including evaluation of vibration perception threshold [195, 198], plantar foot pressure measurements [199], and joint mobility [200].

Angiogenesis

Angiogenesis and vasculogenesis form the mature circulatory system, which is one of the first organs to form and maintains metabolic homeostasis by supplying oxygen and nutrients and removing waste products [27, 131]. An imbalance of the two interrelated processes of angiogenesis and vasculogenesis contributes to the pathogenesis of numerous malignant, inflammatory, ischemic, infectious, immune, and wound healing disorders [131]. In angiogenesis, endothelial cells develop from preexisting blood vessels and migrate and proliferate into a cord-like structure [27] (Table 7.2). Intussusceptive microvascular growth (whereby a mature vessel lumen is divided by the ingrowths of cellular columns) is another component of angiogenesis [27]. Vasculogenesis is the de novo formation of immature vascular structures from the differentiation of progenitor cells [27] (Table 7.3). These newly formed vascular structures mature into capillaries, arterioles, arteries, venules, and veins [27, 108, 109, 201, 202].

Angiogenesis is capillary formation from preexisting ones, which first requires destabilization of the preexisting endothelial tubular structure [27, 211–213]. Often, angiogenesis is caused by tissue injury or neoplastic transformation [27, 214, 215]. During wound healing, neovascularization is new capillary formation to replace damaged capillaries and reestablish the supply of oxygen and nutrients to the wound [27]. During the proliferation phase of wound healing, angiogenesis re-establishes the supply of oxygen and

Table 7.2 Major differences between normal angiogenesis and angiogenesis seen in DFUs

Normal angiogenesis	Angiogenesis in DFU
Proangiogenic cytokines (including VEGF) are released from platelets, monocytes, and fibroblasts	Fibroblasts may become senescent in chronic wounds and lose their ability to provide angiogenic functions [27]
Endothelial cells (ECs) disrupt their interactions with neighboring ECs	Resident ECs of the chronic wound may lose their ability to support new vessel formation [27]
ECs digest the basement membrane and extracellular matrix (ECM) components (via MMPs)	Impaired balance between the accumulation of ECM components and their remodeling by MMPs [160]
ECs, fibroblasts, platelets, smooth muscle cells, and monocytes release more proangiogenic cytokines	The fluid of chronic wounds block cellular proliferation and angiogenesis [203, 204] Impairment of leukocyte function and proliferation occur in hyperglycemia [205]
ECs invade ECM and migrate/proliferate to new vessels	Disruption of new vessel formation disrupts healing at the level of the peripheral wound [27] Hypoxia impairs angiogenesis [206, 207]

Table 7.3 Major differences between normal and vasculogenesis in DFUs

Normal vasculogenesis	Vasculogenesis in DFU
Multipotent adult progenitor cells (MAPCs) differentiate into hematopoietic precursor cells or early endothelial progenitor cells (EPCs) in the bone marrow	Impaired VEGF-induced proliferation response in EPCs [208]
Increased vascular endothelial growth factor-A (VEGF-A) induces vascular endothelial growth factor receptor-1 (VEGF-R1) activation and subsequently increased matrix metalloproteinase-9 (MMP9) secretion	Hyperglycemia-mediated inhibition of VEGF [209]
Increased MMP9 mediates the conversion of membrane-bound kit ligand (mKitL) to soluble kit ligand (sKitL), which mobilizes EPCs from the bone marrow to circulation	Decreased number and function of circulating EPCs impairs healing [131]
Early EPCs in the circulation further differentiate to late EPCs and gain specific endothelial cell (EC) surface markers	Diminished blood supply to peripheral wound [131]
Late EPCs arrive to the site of the new vessel formation and further differentiate into mature ECs or act as a source of proangiogenic cytokines	EPCs demonstrate abnormal mobilization and homing mechanisms in diabetics [210]

nutrients to the wound. Vasculogenesis is the de novo formation of blood vessels from the differentiation of bone marrow-derived precursor cells. Vasculogenesis occurs during both fetal development and in the adult [27]. In the formation of fetal vasculature, primitive mesodermal cells called hemangioblasts form blood islands. These are spatially arranged with cells that differentiate into endothelial cells, or angioblasts, at the periphery. Other cells included in this process are hematopoietic stem cells [27]. An imbalance of angiogenesis or vasculogenesis contributes to numerous pathologies, including malignancies, inflammatory or ischemic, infectious, and immune diseases.

Angiogenesis in Diabetes

During the last decade, the incidence of microvascular complications in DM has rapidly increased [213]. Dysfunctional angiogenesis has been suggested as a common origin for retinopathy, nephropathy, neuropathy, and impaired wound healing [213, 216–220], although the complex pathogenesis of diabetic microvascular complications is still largely unknown [221–223].

VEGF is a key player in a number of diabetes-related pathologies [224]. In some organ systems, elevated VEGF levels act as a pathologic angiogenic stimulus (i.e., ocular neovascularization)

[225], whereas in others, low levels of VEGF activity leads to pathology (i.e., nephropathy, peripheral neuropathy, and wound healing) [140, 226, 227].

Angiogenesis-related complications are implicated in a number of diabetic complications, including diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, coronary artery disease (CAD), and impaired wound healing. As the number of microvascular complications in DM continue to rise, a better understanding of dysfunctional angiogenesis becomes more critical. Further understanding of the role of angiogenesis in these pathologies could provide novel treatments and improve the lives of the millions of patients suffering with diabetes.

Diabetic retinopathy (DR) is one of the leading causes of blindness worldwide [228]. Vision loss occurs due to retinal ischemia, retinal vascular exudation, intraocular hemorrhage, and ultimately, fibrotic complications [229]. Nearly all patients with type 1 DM and over 60% of patients with type 2 DM develop retinopathy during the first two decades of the disease [229]. DR is characterized by abnormal angiogenesis, leading to new vessels that are often immature and play a pathological role in retinopathy, contributing to both vitreous hemorrhage and fibrosis [230]. Increased vascular permeability leads to plasma leakage and the development of macula edema [230]. Diabetic macular edema and retinal neovascularization represent two of the most serious pathological changes in DR [219]. Previous studies have shown that angiogenic factors, including VEGF, play a key role in the development of these two changes [225]. Elevated levels of VEGF in ocular fluids of patients with proliferative DR have been shown [231]. Chronic hyperglycemia increases the synthesis of VEGF (a normally proangiogenic cytokine), contributing to the microvascular abnormalities in DR [232]. Inhibition of VEGF diminishes the microvascular complications seen in experimental animal models [232]. Retinal hypoxia/ischemia upregulates the production of VEGF, which results in abnormal and deregulated angiogenesis [233]. The growth of new vessels from the retina or optic nerve occurs as a result of VEGF release into the vitreous cavity [232]. Further, injection of VEGF into normal primate eyes induces the same pathologic processes seen in diabetic retinopathy, including microaneurysm formation and increased vascular permeability [232]. A key target of current clinical trials is VEGF [225]. Anti-VEGF treatments may represent an alternative adjunctive treatment for proliferative DR. Currently, there are three anti-VEGF agents available: pegaptanib, bevacizumab, and ranibizumab [219].

Diabetic nephropathy (DN) is one of the leading causes of end-stage renal disease [234]. In a pathogenesis similar to DR, abnormal angiogenesis also occurs in diabetic nephropathy [234]. VEGF-A is involved in the normal physiological processes of the kidney [234]. VEGF-A has been shown to be upregulated in the early stages of DN, likely leading to excessive blood vessel formation [235]. However, a decline of VEGF-A in the later phase of DN has also been shown [235]. Two studies have shown beneficial effects of anti-VEGF antibody treatments [236, 237]. However, some theorize that VEGF-A inhibitors could lead to endothelial injury because endothelial cells require VEGF-A in physiological conditions [234]. While anti-angiogenic treatments have prevented the progression of animal models of diabetic nephropathy, further studies are needed before these treatments can be applied to a clinical setting [234].

Diabetes mellitus is one of the greatest cardiovascular risk factors and leads to vascular dysfunction and atherosclerotic disease. The formation of coronary collateral vessels is of functional importance in patients with CAD and is a compensatory mechanism secondary to repetitive or chronic myocardial ischemia [238]. DM was recently shown to be one of the first negative predictors of collateral vessel formation [239]. This reduced collateral circulation in diabetic patients likely contributes to their increased morbidity and mortality [238]. So far, research has shown that coronary collateral vessel formation depends on monocyte function, which is impaired in diabetic patients and VEGF-related signal transduction defects may be the basis of impaired monocyte function in diabetics [240].

Thus, VEGF-A may be a potential therapeutic strategy for reduced coronary collateral circulation in diabetic patients [240].

Treatment for DFUs

Standardized treatment of DFUs includes glycemic control, debridement of necrotic tissue, control of infection, use of moist dressings, protection from pressure or trauma related to ambulation, and adjuvant hyperbaric oxygen (HBO) therapy [131]. In the setting of arterial insufficiency in diabetes, revascularization with return of delivery of oxygen or nutrients is essential and can be accomplished by surgical bypass or percutaneous angioplasty [27]. Unfortunately, this is only feasible at the level of large- and medium-sized arteries and not at the microvascular level [27]. Currently, the only FDA-approved growth factor and cell therapies for DFUs are not routinely used, making management very difficult [2]. Recent study documented that the sooner advanced biological therapies were used, the better the outcome of healing is achieved [241].

Surgical debridement has been a standard of therapy in the treatment of DFUs. Theoretically, surgical debridement aids wound healing by removing necrotic tissue and optimizing the healing capacity of surrounding viable tissue. Despite the fact that surgical debridement is routine practice in DFU treatment, there is incomplete evidence-based science supporting its role [242]. Debridement may work in synergy with other treatment approaches such as cell therapy or growth factors.

Growth factors are promising biological therapies for DFUs and have been useful in combination with surgical debridement. Granulocyte macrophage colony stimulating factor (GM-CSF) and VEGF-A have been considered as treatments to stimulate the bone marrow release of EPCs for wound healing but risks such as acute arterial thrombosis, angina, hypotension, sepsis, and death have complicated their development as treatment modalities [243–248]. Other recombinant angiogenic growth factors have been tested with positive results; these include EGF, FGF, and PDGF (which is an FDA-approved topical wound ointment) [27]. Another study, a randomized placebo-controlled trial, found that granulocyte-colony stimulating factor (G-CSF) increases the release of neutrophils from the bone marrow and improves neutrophil function in DFUs [249]. VEGF-A is an endothelial cell mitogen [250–255], chemotactic agent [256, 257], and inducer of vascular permeability [258–263], and as such is a promising candidate for treatment of chronic wounds. HBO therapy is an adjunctive therapy used to stimulate wound healing when the microvasculature has become compromised but the larger vessels remain open or have been re-vascularized [131]. Tissue-level hyperoxia is the outcome of HBO treatments and it has been supported by many studies [264–269]. In an experimental model of diabetic wound healing, HBO has been shown to work in synergy with chemokines produced by keratinocytes and fibroblasts. Together, HBO and these chemokines recruit endothelial progenitors to circulation and home them to the site of the injury. Thus, adequate presence of chemokines released by keratinocytes and myofibroblasts is important component of successful of HBO therapy [2, 138]. Many current potential treatments are still under research. Gene therapy and stem cell therapy, including a gene encoding VEGF-A, has been reported to enhance healing and angiogenesis in ischemic ulcers in a mouse model of diabetes [270]. Fibroblasts are also a potential therapeutic target: augmentation of fibroblast endogenous cytokine production via transient vector transfection could activate the local angiogenic cascade and promote wound healing [27].

Cell therapy, including cryopreserved human fibroblast-derived dermal substitute, composed of fibroblasts, ECM, and a bioabsorbable scaffold or living skin equivalent composed of keratinocytes and fibroblasts in a native collagen matrix are FDA-approved for the treatment of DFUs. It has been shown that cell therapy promotes healing via the release of various cytokines and growth factors into the local wound milieu [271–273]. This approach to healing is most effective when coupled with surgical debridement of the chronic wound.

Off-loading is a treatment modality that aims to redistribute pressure away from the area of ulceration to improve wound healing in DFUs. The incorporation of pressure-relieving properties in a wound care dressing for the treatment of DFUs is another newer option for treatment [274], where the wound dressing effectively reduces pressure at individual metatarsal heads in patients at risk of diabetic foot ulceration.

Dressings of various types are useful in the management of DFUs. Among the many dressing options, three were recently tested on DFUs in a large randomized controlled trial. The four treatment options (nonadherent, knitted, viscose filament gauze, an iodine-impregnated dressing, both traditional dressings combined, or a new antimicrobial dressing) were found to be similar in efficacy [275]. Collagen-alginate topical wound dressing was found to be more effective than saline-soaked gauze in another randomized controlled trial [276]. The proper dressing modalities, when used in combination with off-loading, debridement, and/or the other more sophisticated biological therapies, are crucial to the treatment of DFUs.

In conclusion, the pathophysiology of wound healing in DM is complex and represents the deregulation and dysfunction of all the phases and cell types involved in the process. In spite of the recent advances, the most effective clinical protocols for the treatment of DFU are yet to be determined. Thus, further research in this area should yield optimization of future therapies for this devastated complication of diabetes.

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Neuropeptides and Diabetic Wound-Healing

8

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Abstract

Diabetes impairs wound-healing, which in turn predisposes patients to develop nonhealing foot ulcers and amputations. Vascular dysfunction, peripheral neuropathy, and immune dysregulation are among the known contributors to nonhealing foot ulcers. In recent years, research efforts have been initiated towards deciphering the role of neuropeptides in wound-healing. In particular, Substance P, neuropeptide Y, and calcitonin gene-related peptide are known to have physiological roles in pain transmission, satiety, and maintenance of vascular tone. Cytokine secretion, immune cell trafficking, and growth factor signaling are some of the mechanisms modulated by peripheral autonomic and sensory neuropeptides through which they affect inflammation and proliferation. Thus, neuropeptides released by cutaneous nerves can directly participate in the healing process by affecting the inflammatory and proliferative phases of wound-healing. We therefore believe that, in diabetic patients with peripheral neuropathy, impaired wound-healing could be a result of neuropeptide dysregulation. The present chapter gives a broad overview of different neuropeptides that could play a fundamental role in the wound-healing process. Additionally, we have discussed different in vivo models that could further help delineate the role of neuropeptides in diabetic wound-healing.

Keywords

Neuropeptides • Inflammation • Cytokines • In vivo models

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A growing body of evidence suggests a regulatory role of peripheral nerves and cutaneous neuroimmunology in wound-healing of normal skin raising significant interest in the research community [1]. Modulation of the healing response is achieved by a complex bidirectional interaction of elements of the local nervous and immune system, which is further controlled through endocrine feedback between both the peripheral as well as the central nervous system [1–3]. Cutaneous nerve fibers and inflammatory cells are known to release neuromediators, including neuropeptides and cytokines, that modulate the activity of specific neuropeptide and cytokine receptors on various skin cell types, including immunocompetent cells, Langerhans cells, endothelial cells, mast cells, fibroblasts, and keratinocytes leading to direct activation of intracellular G-protein signaling cascades [1, 4, 5]. Substance P (SP), neuropeptide Y (NPY), and calcitonin gene-related peptide (CRGP) are neuropeptides commonly involved in the regulation of immune response and subsequent wound-healing. There are other neuropeptides, such as melanocyte-stimulating hormone (MSH) and neurotensin, which are also neuromodulators with a potential role in diabetic wound-healing. These neuropeptides are released from sensory and autonomic nerve fibers as well as from cells of the dermis and epidermis [2]. Various cytokines involved and dysregulated in diabetes, including IL-1, IL-6, IL-8, and TNF-α, are regulated by these neuropeptides [1].

Substance P

Among the neuropeptides implicated in wound-healing, Substance P (SP) is emerging as a potent regulator of cutaneous wound-healing. Angiogenic properties of SP have been shown in both in vitro and in vivo studies. Further SP is revealed to be important in the recruitment of granulocytes to wound sites [6]. SP induces fibroblast proliferation and inhibits fibroblast apoptosis via elevating the expression of proliferating cell nuclear antigen and BCL-2 in burn wounds [7]. Interestingly, SP has shown to be reduced in skin biopsies from both type I and type II diabetes patients [8]. SP gene and protein expression is reduced in a model of type I diabetes, [2]. Further, the enzyme that breaks down SP, neutral endopeptidase (NEP), is elevated in diabetes and the use of an NEP inhibitor has proven to promote wound-healing [9]. In endothelial cells, SP is known to cause vasodilation by releasing nitric oxide, thereby increasing endothelial permeability and extravasation of leukocytes to the underlying tissues [10]. It is strong chemoattractant towards immune cells, increases the expression of endothelial leukocyte adhesion molecule-1 on human microvascular endothelium and leukocyte function-associated antigen-1 (LFA-1) on murine ECs and lymphocytes and can stimulate the production of TNF-α, IL-1β, IL-2, IL-8, IL-6, TGF-beta from T-lymphocytes, macrophages, neutrophils, and fibroblasts [11–23]. Thus by creating a pro-inflammatory microenvironment, SP plays an important role in the inflammatory and angiogenic phases of wound-healing.

Neuropeptide Y

NPY is also implicated in aberrant wound-healing and is a highly conserved 36 amino acid polypeptide, and is one of the most abundant neurotransmitters in the mammalian CNS and PNS [1]. In addition to the nerves, other non-neuronal cells have been shown to express NPY, including megakaryocytes, liver, heart, spleen, and ECs [24, 25]. Diabetes affects the levels of NPY in a more complex way than SP. NPY is mostly studied for its effects on the central nervous system, where NPY induces feeding and conservation of energy and counteracts the effects of leptin. Thus, the majority of NPY-related diabetes studies revolve around its CNS effects [1]. In the hypothalamus of both type I and type II diabetes patients, NPY expression is increased whereas in the skin, in type I diabetes, it is reduced [26–28]. A recent study revealed that NPY plasma levels of type II diabetic patients are increased; however, there is little data about cutaneous NPY expression in these patients. Baseline expression of NPY does not seem to be altered in a diabetic rabbit model of cutaneous wound-healing [2].

Similar to SP, NPY also appears to be pro-angiogenic and modulates elements of the innate and adaptive immune system [1]. In particular, NPY modulates cell migration, cytokine release from macrophages and helper T cells, antigen presentation as well as activation of natural killer cells and antibody production [29–31]. NPY is mainly known to be involved in cartilage and tendon healing, but through its pro-angiogenic receptors NPY-2R and NPY-5R it also affects cutaneous healing [32–35]. The enzyme dipeptidyl peptidase IV (DPP IV) that cleaves NPY into its pro-angiogenic form, which then binds to Y2 and Y5 angiogenic receptors, is increased in aging mice [36, 37]. Similar to SP, NPY is also important for both the inflammatory and angiogenic phases of wound-healing. More studies are required to understand the role of NPY in diabetic wound-healing.

Calcitonin Gene-Related Peptide

CGRP is also found in both, the CNS and the PNS. In the PNS, CGRP is co-stored and co-released with SP from capsaicin-sensitive peripheral afferent neurons and is also a potent vasodilator [38–40]. Similar to NPY, CGRP also has extra-neuronal expression, such as liver, lungs, kidneys, prostate, and testis [41]. In the peripheral tissues, CGRP receptors are found in the heart, vasculature, liver, spleen, skeletal muscle, lung, and lymphocytes [38]. Diabetes is known to reduce CGRP in mice hearts, reduce CGRP-mediated vasodilation in rats and reduce both CGRP and CGRP receptor expression in rat diabetic cardiomyopathy model [42–49]. As another player in wound-healing CGRP promotes angiogenesis by increasing VEGF release from local cells and activating the cAMP pathway [50, 51]. Further, CGRP leads to an increased release of IL-1α and IL-8 from keratinocytes, IL-8 from corneal epithelial cells, IL-1, IL-8, and ICAM-1 expression in airway epithelium, IL-1β, IL-6, and TNF-α in dental pulp fibroblasts, IL-1β, and TNF-α in macrophages and acts as an chemoattractant for T lymphocytes, modulates lymphocyte proliferation and inhibits IL-2 production [52–58]. In animal models of diabetes, CGRP was also reduced in tissues, such as the heart and the dorsal root ganglion, however not much is known about its cutaneous expression [44–46].

Melanocyte-Stimulating Hormone

The family of melanocortins consists of structurally related peptides that are not only involved in the regulation of pigmentation and cortisol production but further regulate food intake, energy homeostasis, sexual behavior, exocrine gland function, and inflammatory responses [59]. a-MSH is derived from proopiomelanocortin (POMC) and is mainly released from the pars intermedia region of the pituitary gland, respectively [60]. However, human skin is also a source of significant a-MSH production [61–63]. Various cell types of the skin, including melanocytes, keratinocytes, fibroblasts, and endothelial cells synthesize a-MSH and express melanocortin receptors (MCRs). In case of a-MSH, it is a-MSH that controls glucose metabolism instead of the other way around [64]. Long-term activation of a-MSH reduces body weight, fatty liver changes, and improves glucose metabolism in a model of diet-induced obesity [65].

Two diabetic rat studies revealed that POMC mRNA in arcuate nucleus, pituitary and the hypothalamus is decreased but cannot be reversed after insulin treatment [66, 67]. a-MSH is known to have anti-inflammatory properties and has shown to attenuate inflammatory pathways that are relevant for inflammatory bowel disease, heart transplantation, and brain inflammation [68–73]. Further, a-MSH downregulates CD86, a major T cell costimulatory molecule, in activated monocytes and increases the expression of the anti-inflammatory cytokine IL-10 in human peripheral blood monocytes and cultured human monocytes. a-MSH inhibited release of TNF-α from LPS stimulated THP-1 monocytes [74]. In human dermal fibroblasts, α-MSH regulates the expression of IL-8 [75], in human peripheral blood monocytes and cultured human monocytes, α-MSH increases the production and expression of the anti-inflammatory cytokine IL-10. In septic

patients, small concentrations of α-MSH added to LPS-stimulated whole blood samples inhibit TNF-α and IL-1β production, in RAW264.7 mouse macrophages, inhibits nitric oxide production induced by LPS and IFN-γ [76–80]. In resting endothelial cells, α-MSH causes an increase in the expression and release of IL-8, in stimulated dermal fibroblasts decreases IL-8 release and in human keratinocytes increases expression of IL-10 [75, 81–83]. In a rabbit model of corneal wound-healing, topical administration of the C-terminal tripeptide (KPV) sequence of a-MSH (a-MSH11–13) improved the healing response [84]. It is evident that a-MSH affects inflammatory pathways and its abundance in cutaneous cells makes it an interesting target for further cutaneous diabetic wound-healing research.

Neurotensin

The tridecapeptide NT is predominantly expressed in the CNS (hypothalamus and pituitary) and in endocrine cells (N cells) of the jejunum and ileum. NT inhibits CNS dopaminergic pathways and stimulates growth of various gastrointestinal tissues as well as adrenal gland, hepatocytes and fibroblasts in the periphery [85]. NT receptors are found throughout the CNS [86]. Evidence suggests that NT may play a role in the pathogenesis of diabetes. Elevated levels and total amounts of NT are observed in the pancreas of obese (ob/ob) mice and the intestine of both ob/ob and diabetic (db/db) mice [87]. Likewise, insulin regulates pancreatic NT concentrations, with elevated NT levels occurring in association with insulin deficiency in ob/ob and db/db mice [88]. However, in another study, NT levels were not different between lean and obese diabetic mice. Further, human studies did not show any difference in NT levels between nondiabetic subjects and lean and obese diabetic patients pre- and postprandially [89, 90]. NT has been reported to affect wound-healing by modulating cell functions of both innate and adaptive immunity [91–95]. NT-positive nerve fibers and NT mRNA are present in the skin. Cutaneous NT activates skin mast cells and leads to release of histamine [96, 97]. NT is associated with various diseases of gastrointestinal tract, thus most research on NT's role in inflammation revolves around diseases of the GI tract. However, there is limited data about the role of NT in the skin.

In human non-transformed colonic epithelial cells, NT stimulates NF-kB-dependent IL-8 expression by increasing IkBa phosphorylation and degradation, p65 phosphorylation and transcriptional activity, and Rho-dependent pathways [98, 99]. In the setting of chronic intestinal inflammation, NT stimulates intestinal wound-healing via induction of the COX2 pathway [100]. NT promotes migration of microglial cell line C13NJ by a mechanism dependent on both PI 3-kinase and MAP kinase pathways via the receptor NTR3 in a brain tissue wound-healing model and a chemotaxis assay [101]. This data underlines the importance of NT as an immunomodulator. At this point, not much is known about the effects of diabetes on NT signaling in the periphery. With respect to NT's role in cutaneous wound-healing, one might expect that NT would enhance wound-healing by increasing IL-8 expression and/or initiating mast cell degranulation.

These studies illustrate that neuropeptides are important players in wound-healing and they do so by affecting the inflammation and angiogenesis phases of wound-healing (Table 8.1). Neuropeptides released from cutaneous nerves, in addition to their classic role as neurotransmitters also affect signaling cascades of different cutaneous cells, such as keratinocytes, melanocytes, fibroblasts, and dermal microvascular endothelial cells (Fig. 8.1).

In Vivo Models of Diabetic Wound-Healing and Neuropeptides

From the above sections, it is clear that neuropeptides are an integral component of the wound-healing cascade. Thus, to evaluate their potential as therapeutic targets in diabetic wound-healing, it is important to understand their mechanisms of actions and their efficacy in vivo.

The most popular in vivo models of diabetic wound-healing are the rodent models. Rodents

Table 8.1 Phases of cutaneous wound-healing affected by neuropeptide–cytokine interaction (Adapted from Pradhan et al. [1, 2])

Neuropeptide	Cytokines affected	Phases of cutaneous wound-healing affected	References
Substance P (SP)	TNF-α, IL-1β, IL-2, IL-8, IL-6, and TGF-β	Early and late inflammation and angiogenesis	[13, 22, 23]
Neuropeptide Y (NPY)	IL-2 and TNF-α	Angiogenesis	[34]
Calcitonin gene-related peptide (CGRP)	IL-1α, IL-1b, IL-8, IL-2, IL-6, and TNF-α	Needs investigation	[52–58]
α-Melanocyte-stimulating Hormone (α-MSH)	IL-8, IL-10, TNF-α, IL-β, IFN-γ, and IL-8	Proliferation, angiogenesis and remodeling	[75–83]
Neurotensin (NT)	IL-8	Needs investigation	[101]

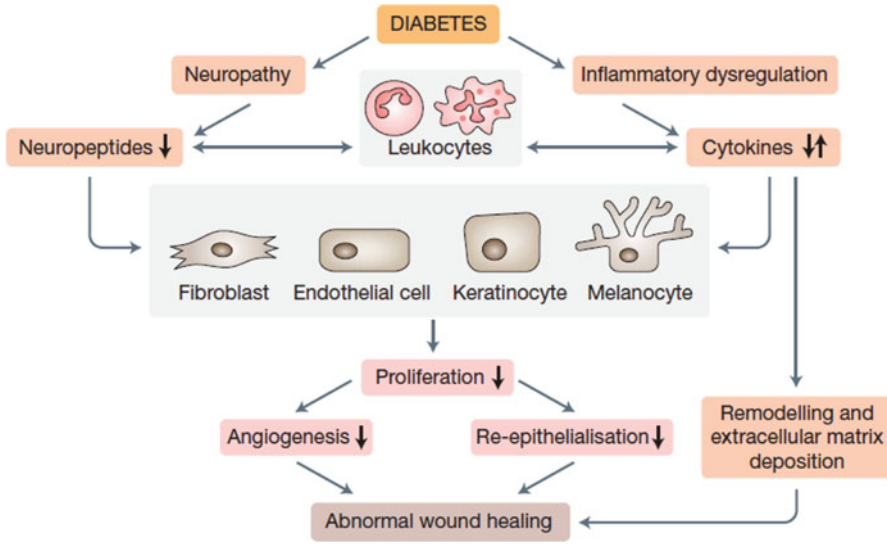

Fig. 8.1 Effect of diabetic neuropathy and inflammatory dysregulation on wound-healing. Diabetes leads to neuropathy and inflammatory dysregulation, which manifests in decreased neuropeptide expression and imbalance in the inflammatory cytokine response. Neuropeptides directly affect leukocytes and monocytes thereby further contributing to the imbalance in cytokine expression. In addition, neuropeptides and cytokines also directly affect endothelial cells and keratinocytes, thereby reducing their proliferation and leading to decreased angiogenesis and re-epithelialization. Decreased angiogenesis and re-epithelialization and dysregulation in remodeling and extracellular matrix deposition (affected by disrupted cytokine expression) result in the final outcome of abnormal wound-healing. (Reprinted with permission from Pradhan et al. [1] *Expert Reviews in Molecular Medicine* ©2009 Cambridge University Press)

are made diabetic using streptozotocin (STZ) or alloxan and full thickness wounds are made on the dorsum. Rodent models are commonly used because of their economic feasibility and shorter reproduction times. Mouse models are used when knock-out and transgenic mice are preferred and rat models are used when more wounds are preferred.

Besides the STZ-induced diabetic models, the db/db (leptin receptor knock out) mouse model is

also commonly employed. Moreover, there are several studies involving different knock out (KO) and transgenic mice where genes important in the wound-healing cascade are investigated. Examples include, b6 integrin KO, insulin receptor KO, redox enzyme p66Shc KO, dioxin receptor AhR KO, stromal-derived factor-1a (SDF-1a) transgenic, suppressor of cytokine signaling (SOCS)-3 transgenic, heme oxygenase-1 transgene [102–108]. In each of these studies, mice are made diabetic using STZ or are on the db/db background.

Similar to mice, most of the diabetic rat models include rats made diabetic by administration of STZ or alloxan. However, compared to mice, there are fewer genetically modified rat models of diabetic wound-healing. The JCR:LA-cp/cp obese rats have been evaluated for model of type II diabetes and show significant reduction in wound-healing [109]. Other genetically modified rat models, such as diabetic BB/O(ttawa) K(arlsburg) rats, a rat strain that represents a close homology to type I diabetes in humans and Otsuka Long-Evans Tokushima fatty (OLETF) rats, a model of type II diabetes are used for studying bone fracture and corneal wound-healing in diabetes [110, 111].

One of the major shortcomings of the rodent models are the anatomical and physiological differences between humans and rodents such as, rodents have a follicular pattern and different hair growth cycle, relatively thin epidermal and dermal layers, are considered "loose-skinned" and have panniculus carnosus because of which wounds heal by contraction and not re-epithelization [112]. Additionally, whereas human wounds often get infected, rodent wounds do not and whereas human wounds take weeks or months to heal, rodent wounds heal within days.

Although there are more than 300 studies in mouse diabetic wound-healing and over 100 studies in rat diabetic wound-healing, to this date, there are only four studies in mice and none in rats that investigate the role of neuropeptides in diabetic wound-healing [9, 113–116].

In a recent study, vacuum-assisted closure-treated wounds in the diabetic mouse model showed a significant increase in dermal and epidermal nerve fiber densities and in Substance P, CGRP, and nerve growth factor expression [115]. In this study, cyclical treatment mode correlated with the largest increase in granulation tissue production, wound surface micro-deformations, and a slightly faster wound closure rate [115]. An excisional wound study in db/db mice demonstrated that compared to wild type nondiabetic littermates, db/db murine skin had significantly fewer epidermal nerves and the wounds took longer to heal [116]. Additionally, exogenous Substance P treatment accelerated wound-healing in both the db/db and their wild type littermate mice [116]. A study by the same group showed that in the db/db mouse, treatment of the excisional wounds with Substance P compared to saline increases leukocyte infiltration in the early period after injury suggesting a role for Substance P induced early inflammation in wound-healing [114]. Moreover, they also showed that the activity of NEP, a cell surface metallopeptidase that degrades Substance P is increased [9]. When its inhibitor is topically applied to the wounds, it enhances wound-healing in the db/db mice [9]. In a rabbit model of diabetic wound-healing, our group has shown that there is decreased gene expression of Substance P in the diabetic rabbit skin compared to nondiabetic and postinjury, both, NPY and Substance P gene expression is decreased irrespective of diabetic status [2].

Among the large animal models, the rabbit and porcine models of wound-healing have been used. Both rabbits and porcines are made diabetic by administering STZ or alloxan monohydrate. In case of the rabbit model, wounds are made in the ear and in the case of porcine model, full thickness wounds are made on the back.

Studies investigating rabbit ear vasculature and innervation date back to 1926 [117]. Rabbit ear skin is similar to human skin and similar to humans has blood vessels that serve as a major heat-exchange surface, controlled by the autonomic nervous system for thermoregulation [118–121]. In addition, the major blood vessels in the rabbit ear lie in a thin skin sheet and are easy to view and manipulate especially when creating an ischemic model of wound-healing (Fig. 8.2). The rabbit ear skin lacks panniculus carnosus and hence the wounds heal by re-epithelization rather

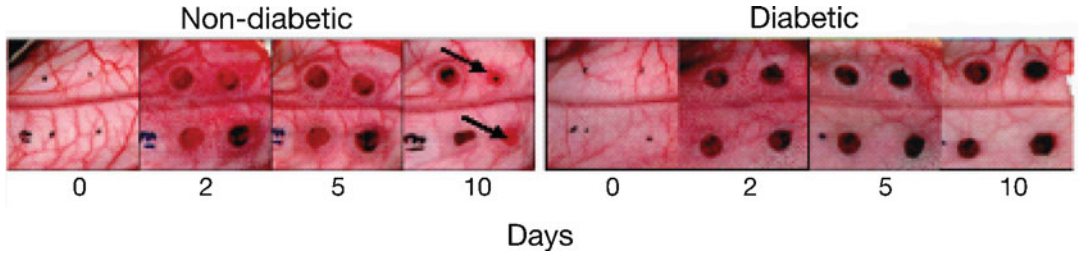

Fig. 8.2 Representative picture of rabbit model of wound healing. *Left*: wounds from nondiabetic rabbits. *Right*: wounds from diabetic rabbits. Day 0 is before injury and days 2, 5, and 10 are postinjury. *Arrows* indicate healed wounds in nondiabetic rabbits. (Reprinted with permission from Pradhan et. al. [2], *Journal of Surgical Research*, Elsevier 2010)

than contraction. In most models, the cartilage in the skin is kept intact and helps in stenting the wound open and further ensures wound-healing by re-epithelization over wound contraction [2].

Anatomically and physiologically, pig's skin is also similar to human skin. Both pig and humans have a thick epidermis, well-developed rete-ridges and dermal papillary bodies, abundant subdermal adipose tissue, similar dermal collagen, vasculature and epidermal turnover time and both lack panniculus carnosus [122]. The differences include that pig skin contains no eccrine glands, and unlike man, apocrine glands are distributed through the skin surface [122].

Several rabbit diabetic wound-healing studies are focused on corneal wound-healing [123–128] and few studies are focused on cutaneous wound-healing [2, 129, 130]. There are some studies in pigs addressing the problem of wound infections in diabetes [131, 132] while others investigating the effects of autologous cell therapy and gene therapy in pig diabetic wound-healing [133, 134].

As described above, there are several studies that describe the neuro-cutaneous connection, yet it is surprising that there is a severe dearth of wound-healing studies that define the connection between neuropeptides and nonhealing diabetic ulcers.

Similar to the lack of neuropeptide diabetic wound-healing studies in rodents, out of about 20 studies in rabbit diabetic wound-healing and ten studies in pig diabetic wound-healing, there is only one study in rabbits and none in pigs addressing the role of neuropeptides in wound-healing [2].

With the ever-growing epidemic of diabetes, complications such as nonhealing ulcers are on the rise and put a serious burden on the economy. Neuropathy and the role of neuroeptides in wound-healing are gaining wide attention. A lot of the studies emphasize the role of neuropeptides in inflammation in different diseases, including cutaneous inflammation. In wound-healing, neuropeptides can modulate both, the inflammatory and angiogenic phases and therefore any imbalance in their expression can alter the outcome of wound-healing. In diabetes, neuropathy is a major complication, which leads to loss of neuropeptides and/or their signaling. Thus, any changes in the neuropeptide pathway can disrupt the cytokine balance with a poor wound-healing outcome.

Several of the neuropeptides have been discovered decades ago and their regulation in diabetes has been known but a direct assessment of their role using animal models is not made nor a direct connection between neuropeptides, wound-healing, and diabetes is clearly outlined. Therefore, more indepth investigation is necessary to dissect this relationship in vivo.

Neuropeptides are promising targets in the quest for developing new therapies for diabetic wound-healing but more translational studies are warranted to delineate their exact mechanisms in diabetic wound-healing.

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Induced Regeneration of Skin and Peripheral Nerves in the Adult

9

Eric C. Soller and Ioannis V. Yannas

Abstract

Injury to the mammalian fetus is reversible during early stages of gestation and the spontaneous wound response is capable of restoring the structure and function of the original organ, a process called *regeneration*. By contrast, the unimpaired response to severe injury in adult mammals is an irreversible *repair* process leading to closure of the injured site by contraction and formation of scar, a nonphysiological tissue. The consequences of irreversible healing at the organ scale are far-reaching: they typically result in an essentially nonfunctional organ.

Numerous approaches have been investigated to restore the loss of organ function in adults following irreversible injury. These strategies include transplantation, autografting, implantation of permanent prostheses, the use of stem cells, in vitro synthesis of the organ, and regenerative medicine (Yannas, Tissue and organ regeneration in adults. Springer; 2001). The last of these strategies is also referred to as *induced organ regeneration*, or the recovery of physiological structure and function of nonregenerative tissues in an organ (also known as de novo synthesis) by use of elementary reactants, such as biologically active scaffolds, either unseeded or seeded with cells.

There is accumulating evidence that the spontaneous healing process of an injured organ in the adult mammal can be modified to yield a partially or completely regenerated organ. Regenerative medicine is an emerging field of study involving the implantation of biomaterials to facilitate formation (regeneration) of tissue in vivo. This field is undergoing rapid growth at this time, as evidenced by observation of regeneration or reported progress in on-going research efforts in a wide range of organs including skin (Butler and Orgill, Adv Biochem Eng Biotechnol 94:23–41, 2005),

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conjunctiva (Hatton and Rubin, Adv Biochem Eng Biotechnol 94:125–140, 2005), peripheral nerves (Zhang and Yannas, Adv Biochem Eng Biotechnol 94:67–89, 2005), bone (Mistry and Mikos, Adv Biochem Eng Biotechnol 94: 1–22, 2005), heart valves (Rabkin-Aikawa et al., Adv Biochem Eng Biotechnol 94:141–178, 2005), liver (Takimoto et al., Cell Transplant 12(4):413–421, 2003) articular cartilage (Kinner et al., Adv Biochem Eng Biotechnol 94:91–123, 2005), urological organs (Atala, Adv Biochem Eng Biotechnol 94:179–208, 2005), and the spinal cord (Verma and Fawcett, Adv Biochem Eng Biotechnol. 94:43–66, 2005).

Keywords

Irreversible injury in skin and nerves • Repair • Skin regeneration • Regenerative similarity • The tissue triad • Anatomically well-defined defect • Synthetic protocol • In Vitro • In Vivo • Induced organ regeneration • Collagen-based scaffolds • Dermal regeneration template • Peripheral nerve regeneration • NeuraGen • Collagen-based scaffolds • Defect closure rule • Spontaneous healing • Contraction • Repair • Contractile fibroblast • Scaffold regeneration

Introduction

Injury to the mammalian fetus is reversible during early stages of gestation and the spontaneous wound response is capable of restoring the structure and function of the original organ, a process called *regeneration*. By contrast, the unimpaired response to severe injury in adult mammals is an irreversible *repair* process leading to closure of the injured site by contraction and formation of scar, a nonphysiological tissue. The consequences of irreversible healing at the organ scale are far-reaching: they typically result in an essentially nonfunctional organ.

Numerous approaches have been investigated to restore the loss of organ function in adults following irreversible injury. These strategies include transplantation, autografting, implantation of permanent prostheses, the use of stem cells, in vitro synthesis of the organ, and regenerative medicine [1]. The last of these strategies is also referred to as *induced organ regeneration*, or the recovery of physiological structure and function of nonregenerative tissues in an organ (also known as de novo synthesis) by use of elementary reactants, such as biologically active scaffolds, either unseeded or seeded with cells.

There is accumulating evidence that the spontaneous healing process of an injured organ in the adult mammal can be modified to yield a partially or completely regenerated organ. Regenerative medicine is an emerging field of study involving the implantation of biomaterials to facilitate formation (regeneration) of tissue in vivo. This field is undergoing rapid growth at this time, as evidenced by observation of regeneration or reported progress in on-going research efforts in a wide range of organs including skin [2], conjunctiva [3], peripheral nerves [4], bone [5], heart valves [6], liver [7], articular cartilage [8], urological organs [9], and the spinal cord [10].

The basic outline of a hypothetical mechanism for induced organ regeneration has become clear. It relies on regenerative studies in three organs (skin, conjunctiva, and peripheral nerves), which started much earlier and have progressed much further than research in other organs. From these studies a pattern has emerged, based on two observations: (a) regeneration was successfully induced, at least partially, when contraction was blocked, following grafting with a class of scaffolds that

were characterized by a very highly specific structure (collectively referred to as "regeneration templates") and (b) when a class of "inactive scaffolds" with slightly different properties than their biologically active counterparts was used, regeneration was thwarted and vigorous contraction ensued. The available data support the hypothesis of contraction blocking as a plausible mechanism for induced organ regeneration in the adult mammal. In almost all such processes, the critical reactant supplied by the investigators was a scaffold, a highly porous, degradable macromolecular solid that has a specific contraction-blocking activity as well as the ability to mimic the in vivo environment, and particularly the stroma, of the organ.

In this chapter, we present elements of a theory of induced regeneration that is organ nonspecific. We proceed by discussing, in order, the macroscopic outcome of irreversible healing in adults, the evidence for induced regeneration, the association between contraction blocking and regeneration, and a proposed mechanism for the regenerative activity of certain scaffolds.

Most regeneration data available to date comes from acute wound models that prove to be far more amenable to control by the investigator than chronic wound models. When healing is unimpaired, the adult mammalian spontaneous healing response to severe acute injury is contraction and scar synthesis. Nevertheless, the results of recent clinical studies indicate that the discussion in this chapter is relevant to severe chronic wounds. Increasingly, FDA-approved versions of collagen-based devices are demonstrating efficacy in the clinical management of these injuries [11–15]. Detailed indications for their use in the treatment of chronic wounds (classified by both anatomy and pathology/diagnosis) have been presented [16].

The majority of available induced regeneration data described in this chapter comes from skin [17–24] and peripheral nerve models [25–34]; these are the two organs that have been studied most extensively in this respect to date. Skin wounds can be studied with relative ease and for this reason studies of skin wound healing comprise the bulk of quantitative wound healing data in the literature. In organs other than skin, wound healing has been studied mostly qualitatively. Nevertheless, the observations made so far form a body of evidence that suggests certain strong similarities, as well as identifying differences, between wound healing in skin and in less studied organs, such as peripheral nerves. Taken together, the wealth of regenerative data for these two very different organs has aided the development of a general theory of induced regeneration that may have value in studies of induced regeneration in other organs as well [1].

Irreversible Injury in Skin and Nerves

The complex inflammatory response of the adult mammal to injury is elucidated by on-going research at the cellular and molecular level. While the formation of an accurate mechanistic perspective of wound healing is essential both in understanding the effect of current clinical treatment and in the development of emergent therapies, an examination of the macroscopic outcome of healing also provides a uniquely valuable viewpoint. An introductory phenomenological discussion of spontaneous wound healing at the tissue level provides a framework that forms a focus for future discussion of detailed cellular/molecular mechanisms and facilitates the derivation of concepts and rules of induced regeneration that may conceivably apply to almost any organ in the body.

Macroscopic Outcomes of Healing: Repair Versus Regeneration

When exposed to injury, in the form of either acute trauma or chronic insult, the organism mounts a spontaneous wound healing process that typically closes the discontinuity in organ mass caused by the injury in a matter of days. Two macroscopic outcomes to injury have been observed experimentally: regeneration and repair. These fundamentally different processes are clearly distinguished by the identity of tissue present in the final state, that is, the newly synthesized tissue that closes the injured site. In the

early mammalian fetus and in many species of amphibians, wound healing is largely reversible and proceeds via *spontaneous regeneration*, a process that restores the structure and physiological function through synthesis of the missing organ structures [1]. Certain adult urodeles exhibit an impressive capacity for spontaneous regeneration: replacement of an amputated appendage occurs by direct outgrowth of the severed cross section (epimorphic regeneration), a reversible process [35].

In clear contrast, severe injury to normal adult mammalian tissue typically results in an irreversible healing response. Spontaneous healing of severe skin wounds proceeds via *repair*, in which the wound closes with a combination of tissue deformation and translation (collectively referred to as contraction) and synthesis of a nonphysiological tissue (scar) in place of the normally functioning tissue that has been injured [1]. By replacing the lost organ mass with scar, the injured organ is condemned while the organism is spared as a result of the healing process. The immediate consequence of irreversible injury is a loss of normal organ function. On a broader scale, skin injury may have additional detrimental effects, such as loss of mobility and lack of social acceptance, e.g., following formation of disfiguring scars from burns. It appears that nearly every adult mammalian organ can be injured irreversibly and the extent of irreversibility seems to depend both on the identity of the tissue injured and the severity of the injury [1].

Regenerative Similarity: The Tissue Triad

Standard pathology texts describe three generic tissue types that comprise the majority of organs in the body: epithelia, basement membrane, and stroma [1, 36–38] (Fig. 9.1). Collectively, we will refer to these three tissue types as the tissue triad for a specific organ. This classification provides a useful framework for comparing the regenerative capacity of specific tissue types from one organ to another. The composition of each member of the triad is markedly different. Epithelial tissue forms a completely cellular covering on every surface, tube, and cavity in the body, performing a wide array of vital functions including protection, secretion, absorption, and filtration. As epithelial tissue is devoid of extracellular matrix (ECM) and blood vessels, it is sustained by the diffusion of nutrients from the underlying vascular connective tissue, or stroma. Epithelia are separated from underlying stroma by the basement membrane (basal lamina), a very thin, noncellular tissue layer, comprising exclusively ECM. The stroma is a connective tissue layer that is vascularized, containing both cells and ECM.

The skin, as one example, consists of the epidermis (epithelia) attached to the basement membrane and the underlying dermis (stroma). Considerable evidence from peripheral nerve studies indicates that Schwann cells function as epithelial cells following synthesis of a completely cellular layer (myelin sheath) around axons [39]. Nerve fibers (Schwann cell-axon units) are attached to a basement membrane that separates them from the outlying endoneurial stroma, a tissue consisting of a vascularized ECM. Further evidence for the epithelial nature of the myelin sheath comes from the observed polarity of Schwann cells which is very similar to that of keratinocytes, the epithelial cells that form the epidermis in skin. In each case, one epithelial cell surface is firmly attached to a basement membrane and another is part of the epithelial tissue, endowed in each case with function unique to the respective organ, that characterizes the epidermis (in the case of skin) or the nerve fiber insulation of peripheral nerves [39].

Tissues that are "regeneratively similar" appear in different organs yet share a common spontaneous healing response, be it regeneration or repair. The spontaneous healing behavior of each layer of the tissue triad in skin and peripheral nerves is well documented and will be briefly reviewed.

Provided the stroma is still intact to facilitate epithelial cell spreading, injury to the epithelial layer of either of the two organs (the epidermis in skin and myelin sheath in peripheral nerves, respectively) results in spontaneous regeneration of the injured tissue by remaining epithelial cells in the defect [1, 40–43]. Following nerve crushing

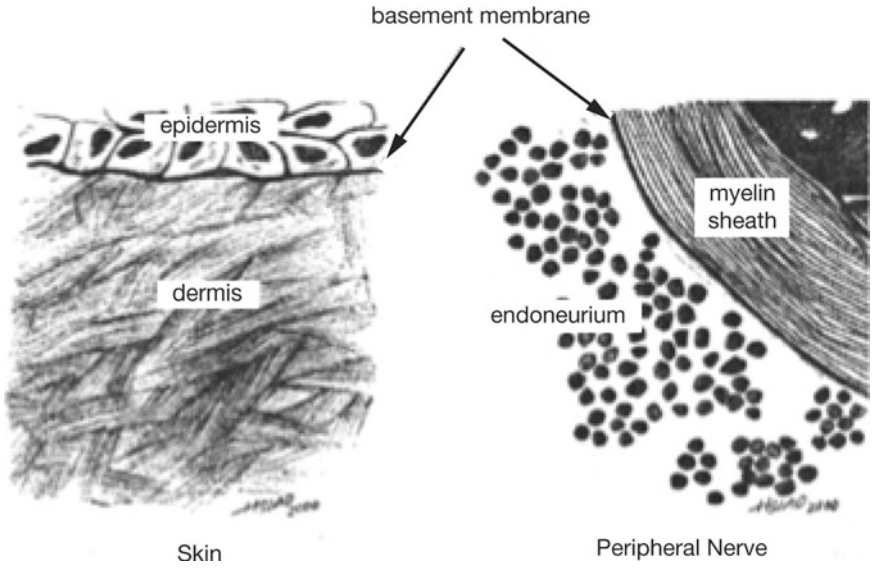

Fig. 9.1 The tissue triad structure in skin and peripheral nerves. The basement membrane (basal lamina), a thin noncellular layer consisting of extracellular matrix, separates the cellular, nonvascular epithelia (epidermis, myelin sheath) from the stroma (dermis, endoneurium) which contains cells, ECM, and blood vessels. Epithelia and basement membrane regenerate spontaneously; stroma does not (Adapted from Yannas, I.V. (2001) Tissue and Organ Regeneration in Adults. Springer, New York)

with myelin disruption but with no injury to the endoneurium, the myelin sheath regenerates spontaneously and no contraction is observed. Similarly, epidermal excision is a reversible injury that closes exclusively by spontaneous regeneration rather than contraction. The epidermis in skin and the myelin sheath in peripheral nerves exhibit spontaneous regeneration, a reversible healing response leading to a full recovery of structure and function, and are therefore regeneratively similar [1]. Injuries that interrupt the continuity of the basement membrane in both organs without injuring the stroma also exhibit spontaneous regeneration by epithelial cells; basement membranes are regeneratively similar in the two organs. However, when a wound is severe enough to cause injury to the stroma of either organ (the dermis in skin or the endoneurial stroma in peripheral nerves), the organism achieves wound closure by a combination of contraction and scar synthesis (irreversible healing response) [44]. The dermis and non-neuronal peripheral nervous tissue, such as the endoneurium, heal by repair; since they are both nonregenerative, they are considered to be regeneratively similar.

In summary, when the spontaneous regenerative capacity of corresponding tissue types in skin and peripheral nerves is directly compared, a useful similarity emerges [1]: Epithelia and basement membrane are regeneratively similar tissue layers, exhibiting a reversible healing response even in the case of severe injury. Likewise, the stroma in both organs is distinctly nonregenerative. Hence, the central objective of induced organ regeneration is synthesis of the nonregenerative stroma.

Experimental Considerations

Importance of an Anatomically Well-Defined Defect

The appropriate experimental volume for studies of induced organ regeneration is the anatomically well-defined defect [1]. The above discussion of

the differential regenerative capacity of the various layers of the tissue triad calls for an experimental injury that is free of nonregenerative tissue. In this manner, the effects of an exogenous regenerative agent on the potential synthesis of nonregenerative tissue can be evaluated without ambiguity. In addition, the experimental volume should also have well-defined anatomical boundaries to reduce contributions from extraneous healing processes occurring elsewhere in the organ (e.g., caused by collateral damage during the surgical procedure) and to improve the reproducibility of the surgical protocol from one animal to the next as well as between independent laboratories. The treatment of the defect should include prevention of loss of extravascular tissue fluid (exudate), which contains important growth factors and regulators that are crucial both to regeneration and to repair. Inability to prevent exudate loss from the injured site radically affects the outcome of both spontaneous and induced healing processes in both skin and peripheral nerves [45–47]. Physical containment is also necessary to prevent detrimental extraneous processes, such as bacterial infection in skin, from interfering with the outcome of the healing response.

For studies of induced regeneration in skin, the most widely used well-defined defect is the dermis-free full-thickness wound in the rodent or swine. In the case of peripheral nerves, the fully transected peripheral nerve in the rat or mouse has been studied extensively [1]. Both the introduction of various grafts or sheet-like covers to skin defects and tubulation to transected nerves using a variety of materials typically imparts significant activity that either assists or hinders regeneration; their use must be controlled carefully.

Synthetic Protocol: In Vitro or In Vivo?

A detailed comparison of the synthetic regeneration processes carried out in vitro and in vivo shows that in studies of skin and peripheral nerves, various protocols for in vitro synthesis have so far resulted largely in the formation of epithelia and the associated basement membrane but not the physiological stroma. By contrast, several protocols conducted in vivo have yielded not only the physiological epithelia and basement membrane, but a near-physiological stroma as well. The following section highlights these observed cases of induced regeneration.

Overview of Induced Organ Regeneration

Evidence of Induced Organ Regeneration in Adults

Studies that started in the early 1970s in the Fibers and Polymers Laboratory at Massachusetts Institute of Technology have shown that the adult mammal can be induced to regenerate selected organs that have been accidentally lost or excised. In every case, it had been established previously that the excised adult organ in question does not regenerate spontaneously; that is, in the absence of experimental intervention, the adult excised site generally closed spontaneously by contraction and scar formation rather than by regeneration. The organs in question were induced to regenerate partially with the aid of certain insoluble substrates (scaffolds) that were optionally seeded with cells (Fig. 9.2).

The most extensive data on induced organ regeneration are available with skin and peripheral nerves (see ref. [1] for a detailed review). Data with other organs from the work of several investigators were presented in a recent volume [3–10]. We review below the induced organ regeneration data obtained in our laboratory.

The three anatomical sites which were induced to regenerate partially were: (1) full-thickness skin wounds, with epidermis and dermis completely excised, in the adult guinea pig, adult swine, and adult human; (2) full-thickness excision of the conjunctiva, with complete excision of the stroma, in the adult rabbit; (3) the fully transected rat sciatic nerve, with stumps initially separated by a gap of 15 mm (later 22 mm and recently 30 mm). A summary of induced regeneration data for the constitutive tissues of each organ is presented in Table 9.1.

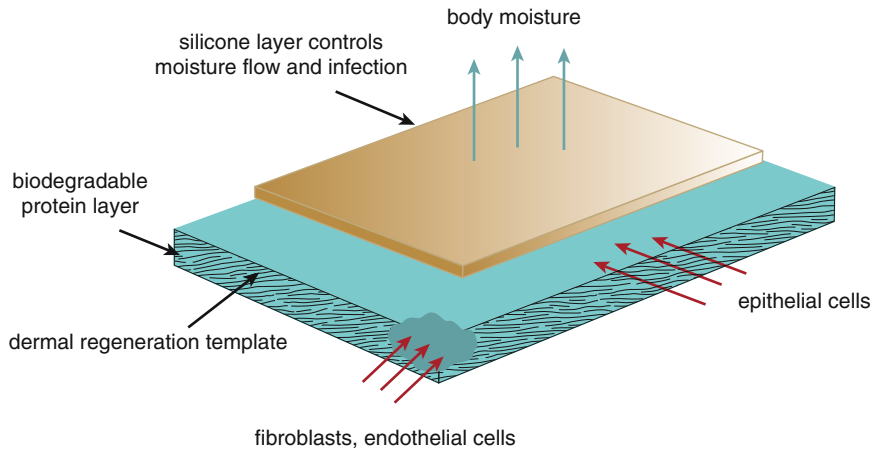

Fig. 9.2 Schematic diagram of a bilayer device that induced regeneration of dermis in full-thickness skin wounds in the guinea pig [7]. The two-layer device consists of a top layer which is a thin film of poly(dimethyl siloxane) that limits bacterial invasion and controls moisture flux to physiologic levels. Underneath is a highly porous scaffold, a graft copolymer of type I collagen and chondroitin-6-sulfate, that induces regeneration of the dermis in the full-thickness skin wound. Regenerative devices based on collagen-glycosaminoglycan scaffolds have been described in a number of patents, either as a cell-free device that induces dermis regeneration or as a keratinocyte-seeded device that induces simultaneous regeneration of dermis and epidermis. Several FDA-approved versions of this device are now used for regeneration of acute and chronic skin wounds in humans (Adapted from Yannas IV, Burke JF, Orgill DP, Skrabut EM. Wound tissue can utilize a polymeric template to synthesize a functional extension of skin. Science 1982;215:174–176)

Table 9.1 Constitutive tissues of skin, peripheral nerves, and conjunctive that were induced to regenerate in adults

Organ	Regeneration observed	Regeneration not observed	Regeneration not studied
Skin (guinea pig, swine, human)	Keratinized epidermis, basement membrane, dermis, nerve endings, blood vessels	Appendages (e.g., hair follicles, sweat glands)	
Peripheral nerve (mouse, rat, cat, monkey, human)	Myelin sheath, nerve fibers (large and small diameter), blood vessels, endoneurial stroma?		Endoneurial stroma? Perineurium
Conjunctiva (rabbit)	Epithelia, conjunctival stroma		Basement membrane

Adapted from Yannas, I.V. (2001) Tissue and Organ Regeneration in Adults. Springer, New York

Observations of induced regeneration in adults made over the years have been tested repeatedly by morphological and functional tests as follows: (a) confirmation of partial regeneration of skin (including both a dermis and an epidermis but lacking skin organelles) was made by histological, immunohistochemical, ultrastructural, and functional studies [7–14]; (b) confirmation of regeneration of the conjunctiva (including the conjunctival stroma) was made using histological data [34]; (c) confirmation of regeneration of peripheral nerves was made using both morphological and functional (electrophysiological and neurological) data [25, 26, 28–33, 48].

The available evidence in the above studies strongly supports the conclusion that these severely injured anatomical sites did not close by contraction and scar formation.

Nevertheless, induced regeneration observed to date is described as "partial" since perfectly

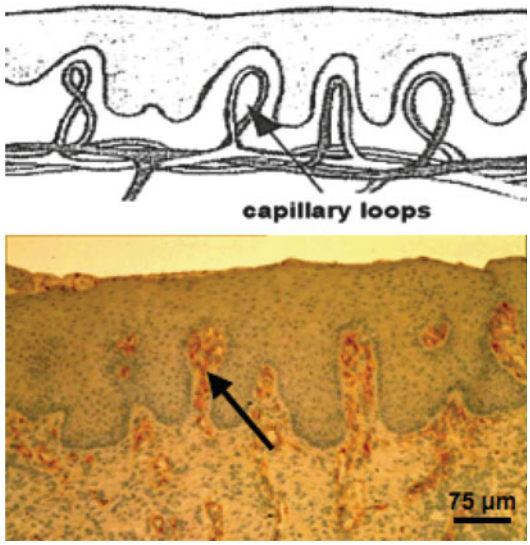

Fig. 9.3 Evidence for induced regeneration of skin using collagen-glycosaminoglycan scaffold. (*Top*) A schematic diagram of physiologically normal skin shows characteristic rete ridges at the dermal–epidermal junction and is contrasted with that of partially regenerated skin in the swine, following grafting with the keratinocyte-seeded dermal regeneration template scaffold (*bottom*). The new skin is not scar, as evidenced by the presence of rete ridges and capillary loops inside the ridges. Immunostaining for Factor VIII 35 days after grafting revealed that capillary loops had formed in the rete ridges of the regenerated dermis (*arrow*) similar to those observed in physiological skin. Bar: 75 µm (*Top*, from Burkitt HG, Young B, Heath JW. Wheater's Functional Histology. Edinburgh, Scotland: Churchill Livingstone; 1993. *Bottom*, from Compton CC, Butler CE, Yannas IV, Warland G, Orgill DP. Organized skin structure is regenerated in vivo from collagen-GAG matrices seeded with autologous keratinocytes. J Invest Dermatol. 1998;110:908–916)

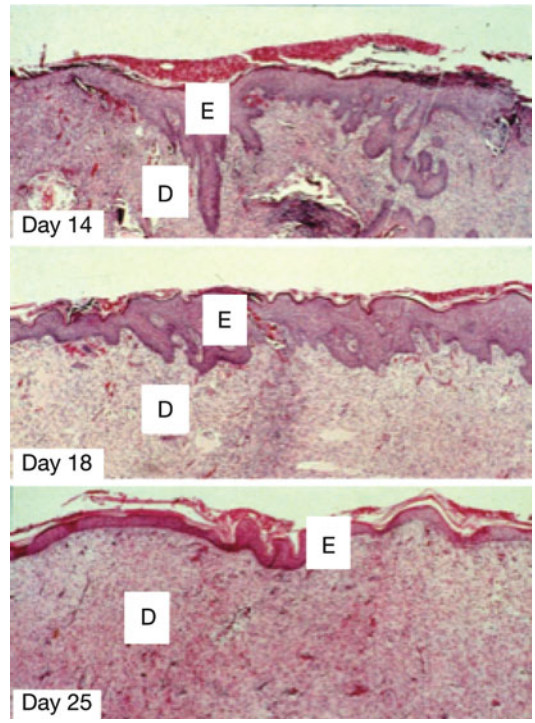

Fig. 9.4 Kinetics of early skin synthesis in the swine with collagen-glycosaminoglycan scaffold between days 14 and 25. In this case, the collagen-glycosaminoglycan scaffold was seeded with autologous keratinocytes before grafting onto full-thickness skin wounds in the swine. Newly formed epidermis is denoted as *E* and the neodermis is denoted as *D*. The scaffolds degrade with a half-life of 15 days (Reproduced from Butler CE, Orgill DP, Yannas IV, Compton CC. Effect of keratinocyte seeding of collagen glycosaminoglycan membranes on the regeneration of skin in a porcine model. Plast Reconstr Surg. 1998;101:1572–1579)

physiological organs have not yet been regenerated. Regenerated skin was histologically and functionally different from scar and identical to physiological skin in almost all respects, including a physiological epidermis, well-formed basement membrane, well-formed capillary loops at the rete ridges of the dermal–epidermal junction, nerve endings with confirmed tactile and heat-cold feeling, and a physiological dermis; however, the regenerate lacked certain organelles (hair follicles, sweat glands, etc.). Evidence for the induced regeneration of partial skin is presented in Fig. 9.3 and the kinetics of this process are presented in Fig. 9.4. The supportive data for induced regeneration of peripheral nerves is presented in Fig. 9.5.

Clinical Experiences with Collagen-Based Scaffolds

The clinical significance of induced regeneration studies is readily apparent. Two collagen-based regenerative devices have been approved thus far

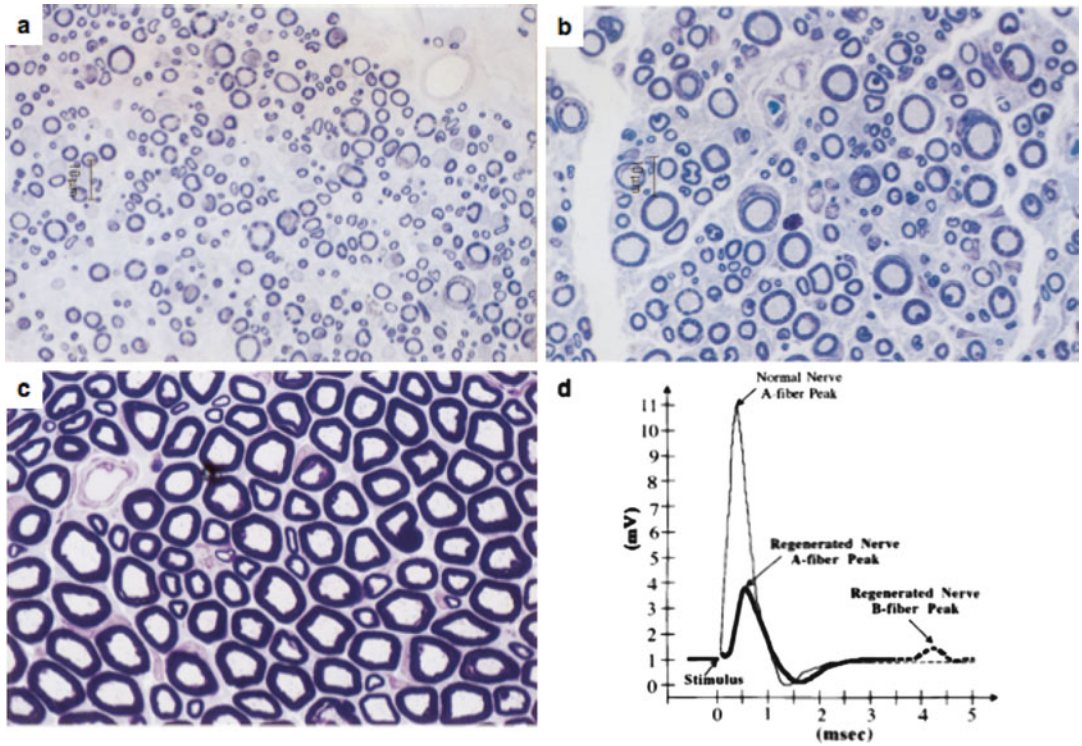

Fig. 9.5 Evidence of induced regeneration of peripheral nerve using collagen-based nerve regeneration template. Histological micrographs of nerve tissue postfixed with osmium tetroxide and stained with toluidine blue. The magnification for each micrograph is the same; scale bars, 10 μm. (**a**) Tissue regenerated through the midportion of a matrix-filled large-pore collagen (LC/M) implant at 30 weeks. Note the large number of axons in this cross-section with the majority of axons being small in diameter. The largest axons have diameters of approximately 7 μm. Many Schwann cells are visible with some actively participating in myelination. The blood vessel that is visible in this micrograph was characteristic of the caliber of most vessels present in the regenerated tissue. (**b**) Tissue regenerated through the midportion of a LC/M implant at 60 weeks. Compared to 30 weeks, the axons are much larger (diameters up to 12 μm) and have thicker myelin sheaths. Also, fewer small diameter axons are visible. Few nonmyelinating Schwann cells are visible at 60 weeks. (**c**) Normal nerve tissue from the level of the lesion is shown as a control. Note the number of large diameter fibers and the thickness of the myelin sheaths compared to the regenerated nerves. (**d**) Typical oscilloscope tracings of A-fiber and B-fiber compound nerve action potentials for normal sciatic nerve and nerve regenerated through a LC/M implant at 60 weeks postimplantation. The A-fiber peak for the regenerated nerve has a significantly smaller amplitude than the normal nerve control. This was typical of all regenerated groups. By contrast, the conduction velocity of the regenerated nerve, although significantly slower than normal, was approaching normal values. The latency is measured along the *x*-axis from the stimulus to the peak and then combined with the constant distance between electrodes to determine conduction velocity. The *dashed line* indicating that the B-fiber peak has been added on to the tracing for reference. Note that the normal nerve tracing has no visible B-fiber peak. In the regenerated nerves, the B-fiber peak was similar and visible in all groups (Reproduced from Chamberlain LJ, Yannas IV, Hsu HP, and Spector M. Collagen-GAG Substrate Enhances the Quality of Nerve Regeneration through Collagen Tubes up to Level of Autograft. Exp Neurol 1998: 154: 315–329)

by the Food and Drug Administration (FDA), one each for the regeneration of skin and peripheral nerves. Increasingly, these devices are establishing themselves as a viable alternative to autografting.

Skin Regeneration with Dermal Regeneration Template®

In 1996, the FDA approved the Integra Dermal Regeneration Template® (DRT, described briefly earlier), as an urgent treatment modality for

patients suffering from severe burns. Since that time, DRT has been approved by regulatory agencies in several other countries. In 2002, the FDA-approved DRT for a second application: restorative or reconstructive surgery of skin scars. The efficacy of DRT for the induced regeneration and treatment of chronic and pathological deep skin ulcers (chronic skin wounds) has been established, and modified versions of this device have been designed specifically for the treatment of these wounds. DRT has been studied recently by several clinical investigators [49–55].

Recent reports demonstrate the efficacy of the DRT in healing foot wounds in diabetic patients [11–16]. A recent study of 30 diabetic patients who underwent surgical debridement of diabetic foot wounds followed by grafting with DRT reported an 86.7% healing rate and a significantly more distal level of amputation ($p<0.003$). A recent retrospective review of 105 patients with diabetic foot ulcers receiving DRT for lower extremity salvage indicates DRT as a viable option for stable closure of these wounds in patients with low risk of amputation. DRT efficacy for patients with an already high risk of amputation (based on available blood supply and presence of infection) seems to be limited. In another study, 111 patients received DRT grafting as a method of closure for selective refractory pathological wounds. Patients were treated predominantly in an outpatient setting with an average healing time of 7 months. Detailed indications for the use of Integra DRT in the treatment of chronic wounds (classified by both anatomy and pathology/diagnosis) have been presented [11–16].

Using a DRT has the potential to replace the need for a full-thickness autograft in a patient population already suffering from large and deep wounds, in those patients where a simplified reconstruction can be designed, and in those in whom less scarring may be desired [56].

Peripheral Nerve Regeneration with NeuraGen™

In 2001, Neuragen®, an early version of the collagen-based tubular devices that have been described above, was approved for the regeneration of peripheral nerves to treat individuals suffering from paralysis of the extremities. Further studies have shown that, as with studies of skin regeneration [4], the structure of collagen requires extensive optimization in order to increase the regenerative activity of this natural protein. One such study identified an optimized version of the device: a cell-permeable collagen tube with controlled degradation rate, higher cell-permeability, and an overall superior quality of regeneration [30].

Recently a multicenter human trial (using randomized, blind, parallel groups), compared the NeuraGen™ nerve guide to direct suturing repair (control group), which is the current clinical gold standard for treatment of short gap injuries [58]. The study followed 32 patients who had complete traumatic nerve injuries to the median and/or ulnar nerves in the distal third of the forearm over 2 years. Patients treated with the collagen devices had significantly lower postoperative pain scores than controls at early time points and at completion of the study demonstrated sensory and motor function performance equal to the direct repair group. Taken together, the results indicate that the collagen nerve guide tube is a realistic alternative to conventional end-to-end nerve repair, but requires extensive redesign in order to optimize the regenerative activity of collagen, thereby making it useful at longer gap lengths.

Limitations of Collagen-Based Scaffolds as Regenerative Devices

As stated earlier, these clinically approved devices do not induce regeneration of entirely normal organs. For example, skin regenerated by the use of collagen-based scaffolds lack several appendages (sweat glands, hair follicles). Future work may focus on speeding the rate of cell migration and angiogenesis within the device (angiogenesis peaks in 7–14 days in a murine model) with the goal of improving regeneration, increasing the safety profile of the device, and decreasing the risk of infection [81]. Peripheral nerves that regenerated with tubular collagen-based scaffolds exhibit conduction velocity profiles that are somewhat slower and weaker than with normal nerves (although scaffolds that have been recently synthesized, but are not commercially available, improve significantly on the clinically available device).

The Defect Closure Rule

Careful review of the literature suggests that no more than three distinct processes are used to close an anatomically well-defined defect (dermis-free defect) in skin wounds: contraction originating from the edges of the defect, scar formation by stromal fibroblasts (followed by epithelialization of scar), and regeneration.

Kinetic data extending continuously over lengthy periods are rarely available from regeneration experiments and often difficult to compare from one study to another. One approach to studying the regenerative activity of exogenous agents on the healing process is to establish two standardized configuration states (e.g., an initial and a final state) and to evaluate the total change that is caused during this fixed period in the healing process. In the absence of kinetic data, the *defect closure rule* bridges the gap by presenting a quantitative description of the healing process through comparison of snapshots of the initial and final stages of wound healing. The initial state of configuration is the anatomical description of the recently generated defect, characterized by the loss of structural continuity in one or more tissues, the beginning of exudate flow, and the loss of physiological homeostatic control of the organ. As defect healing progresses, the original area, A_0, eventually diminishes spontaneously due to one or more of the three processes mentioned above. The area of the closed defect (the closed wound) comprises tissues that result either from contraction (fractional amount, $\%C$), scar formation ($\%S$), or regeneration ($\%R$) and the configuration of the final state can be described by the following simple relation, called the defect closure rule:

$$C + S + R = 100. \qquad (9.1)$$

Equation 9.1 states that the defect closure in any organ can be described by only three outcomes: contraction, scar formation (neuroma or fibrosis), and regeneration (partial or total).

For the idealized case of early fetal wound healing (spontaneous regeneration), contraction and scarring is absent (C, $S = 0$) and

$$R = 100 \quad \text{(regeneration)}.$$

For normal defect closure in adult mammals following irreversible injury (repair), regeneration is absent ($R = 0$) and

$$C + S = 100 \quad \text{(repair)}.$$

The literature describes several assays to determine the configuration of the final state (recently closed defect) [1]. Functional assays can be used to qualitatively identify the physiological nature of the tissue and assist in providing a quantitative measure of its incidence in the final state in terms of the numerical values of these three quantities (C, S, or R). The defect closure rule may be interpreted as a conservation principle: provided that the magnitude of two individual terms (e.g., C and S) has been determined, the magnitude of the remaining process may be calculated. Defect closure data is expressed using the following convention: ($\%C$, $\%S$, $\%R$).

The defect closure rule is useful in evaluating the activity of unknown reactants as inductive agents of regeneration. This quantitative description of the structure and function of the injured organ at its final state has shed interesting light on the relationship between the characteristic elements of the adult healing response (contraction or scar synthesis, or both) and regeneration.

Prevalence of Contraction During Spontaneous Healing

In the skin, the defect closure rule has been used to present data on the configuration of the final state following spontaneous healing of the anatomically well-defined defect (dermis-free defect) in several species. In all cases of spontaneous healing of full-thickness skin wounds, it was ensured that the contribution of regeneration to defect closure was negligible ($R = 0$). Skin contraction was measured directly as the reduction in initial wound surface area by inward (centripetal) movement of skin from the margins of the wound. Scar formation was studied qualitatively by histology. In a few cases, scar formation was confirmed quantitatively by the use of laser light scattering, used to measure the average degree of

collagen fiber orientation and thereby deduce on the identity of the tissue present in the healed injury site [60]. Values for the percentage of initial defect area closed by epithelialized scar (S) were determined using the simplified defect closure rule for repair ($S = 100 - C$).

The contribution of the various methods of defect closure in anatomically well-defined defects is species-dependent. In rodents, where the integument is mobile, contraction is by far the main engine of closure of skin wounds, while scar formation has been shown to be quantitatively much less important.

The spontaneous healing of a full-thickness skin wound in the guinea pig is characteristic of several rodents and lagomorphs (rabbits) and results in the following final state configuration: [91, 9, 0] [7, 8]. In general, $C \gg S$ and defect closure for adult rodents and rabbits reduces to $C \approx 100$.

In humans, where the integument is tethered more securely onto subcutaneous tissues, contraction and scar formation contribute approximately equally to wound closure. Experimentally, the spontaneous healing of full-thickness skin defects in the human ($R = 0$) results in a final state represented by [37, 63, 0] [59].

In the absence of direct quantitative observations, histological analysis was used to describe the closure of the fully transected peripheral nerve in the adult rat. Spontaneous healing results in reduction of the initial area of cross sections of nerve trunks by 95% with neuroma formation (neural scar) accounting for the remaining 5%. The resulting estimation of the final state configuration was [95, 5, 0] [1].

The contraction of a wide array of organs in response to trauma is well documented in both animals and humans, yet these reports are almost exclusively of a qualitative nature [57, 61–80]. The organ in which contraction has been studied systematically to date is the skin. Despite the dearth of widespread quantitative data, the prevalence of contraction must not be overlooked; it appears to be a critical outcome of the spontaneous healing response throughout the adult organism.

The Antagonistic Relation Between Contraction and Regeneration

The characteristic elements of the adult healing response (contraction or scar synthesis, or both) must be controlled in order for induced regeneration to occur. Extensive data, including empirical data on the final state of the defect in response to various reactants, suggest that during healing of a severe injury, contraction antagonizes regeneration [1].

Induced regeneration of skin, a peripheral nerve trunk, and the conjunctival stroma was accompanied in each case by direct observation of a significant reduction in contraction as a mode of defect closure. Conjunctival and peripheral nerve regeneration studies were guided by earlier studies of skin regeneration. Partial skin was first induced to regenerate in the adult guinea pig. The spontaneous healing behavior of the untreated dermis-free defect in this organism resulted in a final configuration of [91, 9, 0]. Grafting an identical well-defined skin defect with a highly porous copolymer of type I collagen and chondroitin 6-sulfate (referred to as a dermis regeneration template, DRT) (Fig. 9.6a) abolished scar synthesis and led to the regeneration of a small mass of dermis and subsequent synthesis of an overlying epidermis within the defect. In the context of the defect closure rule, the regenerative activity of the cell-free DRT on the configuration of the final state [1] was as follows:

$$[92,8,0] \rightarrow [89,0,11] \quad (\text{DRT}).$$

In addition, the DRT led to a significant delay in wound contraction over 25 days.

When a DRT seeded with keratinocytes (KC) was grafted into an identical defect, the result was much more pronounced:

$$[91,9,0] \rightarrow [28,0,72] \quad (\text{DRT} + \text{KC}).$$

KC-seeded DRTs accomplished rapid wound closure through partial regeneration of skin (simultaneous synthesis of a physiological dermis and epidermis, described earlier) and completely arrested contraction at 35–40 days [1].

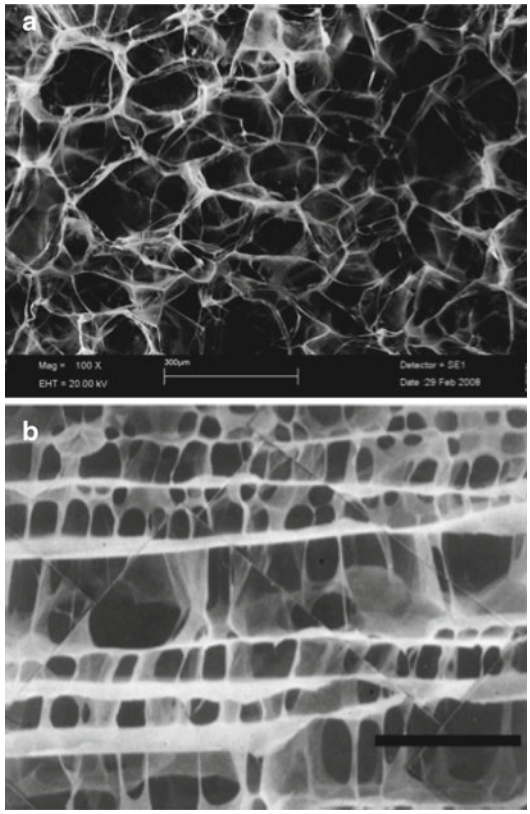

Fig. 9.6 (**a**, *Top*) A scaffold that has induced regeneration of the dermis in animals and humans. Composition: graft copolymer of type I collagen and chondroitin 6-sulfate. Scanning electron micrograph. Pore-channel orientation is almost completely random. Average pore diameter, 80 µm (Courtesy of E. Soller, MIT). (**b**, *bottom*) Peripheral nerve was induced to regenerate across a 15-mm gap (and eventually longer gaps) in the rat sciatic nerve using this scaffold as a bridge between the two stumps inside a silicone tube. In later studies, the chemical composition of this scaffold was changed to GAG-free type I collagen. Pore-channel orientation along the major nerve axis. Scanning electron micrograph. Average pore diameter, 20 µm

The cell-free DRT that induces partial skin regeneration comprises the regenerative component of the two-layer device (Integra DRT®, Fig. 9.6a) approved by the FDA for restoration of a physiological epidermis and dermis in patients suffering from severe burns as well as those undergoing plastic and reconstructive surgery of the skin, as described in an early study [21] and reviewed recently [81].

Growth factors [82, 83], epidermal cell suspensions, and cell sheets [84] exhibited negligible regenerative activity when added to full-thickness skin wounds in other rodent models. These reactants did not significantly alter the configuration of the final state or the extent of contraction delay. Similarly, a number of synthetic polymer scaffolds [85, 86] failed to induce physiological dermis (or skin) regeneration. These observations focus attention on the mechanism of scaffold regenerative activity, to be discussed later.

Quantitative studies of induced regeneration of peripheral nerves were conducted in the adult rat. The spontaneous healing behavior of the untreated transected peripheral nerve in this organism resulted in a final configuration of [95, 5, 0] that was estimated using histological analysis. Insertion of the fully transected nerve stumps into a silicone tube filled with a collagen-based tubular regeneration template (referred to as a nerve regeneration template or NRT, Fig. 9.6b) resulted in reduced contraction (as determined by histological analysis of cross-sectional areas of regenerates) and partial regeneration over a 10-mm gap length [30, 31]. Contraction was abolished and the quality of regeneration improved significantly when the NRT was used in conjunction with a degradable collagen tube. In the context of the defect closure rule, the regenerative activity of the NRT in each experimental configuration can be evaluated by inspecting the estimated characteristics of the final state, as follows (the arrow indicates the change observed following use of the scaffold):

$$[95,5,0] \rightarrow [53,0,47] \quad \text{(NRT inside silicone tube)},$$
$$[95,5,0] \rightarrow [0,0,100] \quad \text{(NRT inside collagen tube)}.$$

The relative importance of each method of defect closure (*C*, *S*, and *R*) changes during animal development. A sharp change occurs during the fetal-adult transition in mammals (roughly during the third trimester of gestation), in which contraction replaces regeneration as the dominant method of closure [87–89]. Similarly, as amphibian (frog) development progresses, contraction becomes a more prominent method of wound closure, as regeneration recedes and scar formation becomes more evident [90, 91].

While scar has been widely considered, the key barrier to regeneration in adults, quantitative study reveals that contraction is the dominant mode of spontaneous closure in skin and peripheral nerve defects. Studies of induced regeneration in skin, peripheral nerves using analogs of the ECM indicate that scar formation is a process that is secondary to contraction: in studies of induced regeneration in these organs, when contraction was even slightly inhibited, scar formation was totally abolished [1].

$$[92,8,0] \rightarrow [89,0,11] \quad (\text{skin}, \text{DRT}),$$
$$[91,9,0] \rightarrow [28,0,72] \quad (\text{skin}, \text{DRT} + \text{KC}),$$
$$[95,5,0] \rightarrow [53,0,47] \quad (\text{peripheral nerve}, \text{NRT in silicone tube}),$$
$$[95,5,0] \rightarrow [0,0,100] \quad (\text{peripheral nerve}, \text{NRT in collagen tube}).$$

Suppression of contraction in certain cases of impaired healing, e.g., following use of pharmacological agents, such as steroids was not accompanied by regeneration, indicating that suppression of contraction alone did not suffice to induce regeneration [1].

The available evidence supports the theory that selectively suppressed contraction in adult defects is required, but not sufficient to induce regeneration of skin and peripheral nerves. This can be expressed in the context of the defect closure (9.1) rule as follows:

$$\Delta R > 0 \text{ and } S \rightarrow 0 \quad \text{if } \Delta C < 0. \qquad (9.2)$$

This condition describes an antagonistic relationship between contraction and regeneration in the closure of a defect. It suggests that successful induced regeneration strategies consist of reactants that block contraction without blocking other aspects of the healing process.

Repair: Mechanism of Contraction

Similarities in the mechanistic hypotheses for inducing regeneration of skin and peripheral nerves originate in their common response to irreversible injury. Both organs spontaneously respond to injury by recruiting contractile cells that, if not properly suppressed, drive closure of the defect by contraction and scar synthesis rather than by regeneration. Contraction of skin defects starts from a cell cluster at the edge of the defect and later extends across the entire defect area. In peripheral nerves, contraction primarily results from the activity of a circumferential sheath of contractile cells.

The Contractile Fibroblast Is the Main Cell Type Associated with Contraction

The well-documented, macroscopic contraction that drives the closure of skin defects finds its origin at the cellular scale, arising from the individual contribution of contractile forces generated by differentiated myofibroblasts (MFB) [92–98]. The current consensus is that MFB that are present in granulation tissue following skin wounding derive directly from fibroblasts and comprise an intermediate, contractile, cellular phenotype between the fibroblast and the smooth muscle cell [99]. There is also evidence that undifferentiated fibroblasts may contribute to macroscopic contraction by applying traction to the ECM very soon after coming into contact with it [100–103].

In response to external tension, fibroblasts exert sustained isometric force on their surrounding environment via a Rho/Rho-kinase (ROCK)-mediated, actomyosin contractile apparatus [104–106]. This 3D, transcellular structure consists of bundles of actin and nonmuscle myosin microfilaments called “stress fibers.”

Of the many ultrastructural and biochemical factors that distinguish MFB from their fibroblast precursors, the most useful operational distinction of MFB differentiation is expression of the α-smooth muscle actin (α-SMA) phenotype [107–109]. Stress fibers of immature MFB (called proto-MFB) contain only beta- and gamma-cytoplasmic actins [89]. Additionally, differentiated MFB exhibit stress fibers typically arranged parallel to the long axis of the cell, nuclei which consistently show multiple indentations or deep folds, and two cell-matrix adhesion macromolecules (vinculin and fibronectin) [107–109].

Simplistically, the myofibroblast differentiation process can be described as a positive feedback loop that requires the concurrent action of at least three factors: the cytokine transforming growth factor-beta1 (TGF-β1), the presence of mechanical tension, and the ED-A splice variant of cellular fibronectin (an ECM component) [92]. Fibroblasts respond to the development of mechanical tension by upregulating TGF-β1 production and expressing the α-SMA isoform; in turn, α-SMA expression strengthens the contractile apparatus and increases tension development [92]. Recent work suggests that mature MFB in skin granulation tissue link their cytoskeletons together using cadherin proteins, which allow them to generate even higher levels of force to drive wound closure [109].

Mechanism of Scaffold Regenerative Activity

Structural Determinants of Scaffold Regenerative Activity

Scaffolds that induce regeneration of partial skin (Fig. 9.6a) possess a highly specific structure that is distinctly different in pore structure and degradation rate from scaffolds that regenerate peripheral nerves (Fig. 9.6b). The nature and duration of the contractile response as well as the structure of the two organs differ greatly as do the values for several of the structural parameters of the early scaffolds that were used to control contraction and induce regeneration in each organ (Table 9.2). The scaffolds are type I collagen-based yet they differ in average pore diameter (higher in the case of the DRT), the pore-channel orientation (axial for the nerve guide, random for the DRT), and degradation rate (a higher average molecular weight between cross-links, *M*c (kDa) in the nerve guide leads to faster degradation).

In skin wounds, the mechanism of induced regeneration has been elucidated through careful modulation of the DRTs structural properties that impart contraction-blocking activity. DRTs that actively block contraction in skin wounds (and induce regeneration) have structural properties that accomplish three main processes: (1) reduction in MFB number present in the wound, possibly due to inhibition of TGF-β synthesis, leading to downregulation of myofibroblast recruitment; (2) blocking orientation of MFB axes in the plane of the defect where macroscopic contraction is observed; and (3) ensuring that DRT degradation time is sufficiently long to ensure that contraction blocking persists for the duration of the interim MFB contractile response but not so long as to interfere with key regenerative processes.

1. *Apparent downregulation of TGF-β synthesis.* The quaternary structure of collagen fibers is a requirement for the aggregation of platelets, an early component of the wound response. Platelet aggregation initiates a cascade of events that include the release of the cytokine TGF-β1, one of the main inductors of the myofibroblast phenotype. Collagen fibers in the DRT maintain their tertiary (triple helical) structure but are practically free of banding (due to treatment with acetic acid during scaffold preparation). DRT apparently disrupts platelet aggregation within the defect, reducing production of TGF-β1, and the recruitment of contractile MFB to the wound site [110].
2. *Blocking orientation of MFB axes in the plane of the wound as well as MFB–MFB binding*. Contraction of wound edges appears to require orientation of MFB axes in the plane of the wound as well as MFB–MFB binding and MFB–ECM binding. MFB binding on the extensive surface of the highly porous 3D scaffold inhibits such orientation as well as inhibiting MFB–MFB and MFB–ECM binding. It is suggested that these mechanisms are additionally responsible for contraction blocking by the scaffold. According to this suggested mechanism, contraction blocking requires extensive MFB binding onto a sufficiently large scaffold surface, which must take place via specific integrin–ligand interactions. Fibroblasts bind onto a specific GFOGER ligand on a collagen surface via the α1β1 and α2β1 integrins [111]. When other structural properties are held constant, the ligand density

Table 9.2 Structural determinants of regenerative activity of CGSs

Structural parameter required for regenerative activity	Skin regeneration[a]	Nerve regeneration[b]	Structural feature hypothetically responsible for contraction blocking
Type I collagen/GAG (w/w) residual collagen fiber banding	98/2 approximately 5% of native collagen	98/2 approximately 5% of native collagen	Ligand identity Reduction in recruitment of contractile cells
Average molecular weight between cross-links (kDa)	5–15	40–60	Controls duration of undegraded scaffold during contraction
Average pore diameter (μm)	20–120 random	5–10 axial	Ligand density
Pore-channel orientation			Ligand orientation

[a]Approximate levels of structural determinants observed in skin regenerative studies conducted by grafting the scaffold on a full-thickness skin wound (Yannas et al. [20])
[b]Approximate levels of structural determinants observed in peripheral nerve regeneration studies performed by inserting the scaffold inside a nerve conduit (the conduit connected the two stumps of the transected nerve across an experimental gap of defined length) (Chang et al. [27]; Chang and Yannas [28])
Adapted from Yannas et al. [81]

of a scaffold increases with decreasing average pore size (since the specific surface area of the scaffold available for attachment is thereby increased). An appropriate ligand density appears to be necessary to disrupt extensive MFB–ECM binding responsible for the onset of macroscopic contraction in skin wounds (Fig. 9.7).

When MFB bind to specific DRT integrins that are distributed evenly in a 3D, interconnecting porous network, the axes of their contractile apparatus becomes disoriented. At the cellular level, the randomized configuration of the preferential contractile axes that individual MFB adopt in the presence of DRT leads to approximate cancelation of the macroscopic mechanical forces that lead to 2D contraction and scar synthesis in ungrafted skin wounds. When the pore diameter of DRT is increased much beyond the level of 120 μm, the effective DRT ligand density drops to a value that does not provide sufficient binding of MFB and the contraction-blocking activity of the scaffold is lost [1, 109, 112]. Similarly, a minimal average pore size exists that is necessary to ensure MFB migration inside the scaffold. According to this interpretation if the pore size is too small, MFB does not infiltrate the scaffold, MFB–DRT ligand bonds do not form, and MFB contractile activity is not canceled. Experimentally, the highly planar orientation of myofibroblast axes that is characteristic of the spontaneous contractile response in ungrafted skin wounds is negligible in the presence of DRT [113].

3. *Duration of DRT in an undegraded state over the entire contraction process*. It is known that the regenerative activity of the scaffold depends sensitively on its degradation rate during skin regeneration [114] as well as during regeneration in the PNS [96]. To explain the data, it has been hypothesized that the DRT is required to undergo a process of *isomorphous tissue replacement*, in which the regenerate (dermis or nerve tissue) is synthesized at a rate which is of the same order as the rate of degradation of the DRT. The requirement for an optimal scaffold duration may reflect the need to have the scaffold persist in an undegraded (insoluble) state over a period that matches the length of the contraction process in skin wounds and nerve wounds, thereby ensuring that the contraction-blocking activity is operative when it matters. In skin wounds, the optimal half-life of degradation (t_b) for DRT in vivo is 14 days, roughly matching the irreversible contraction response in ungrafted wounds (t_h) [1, 112]. In peripheral nerve wounds, the optimal degradation half-life

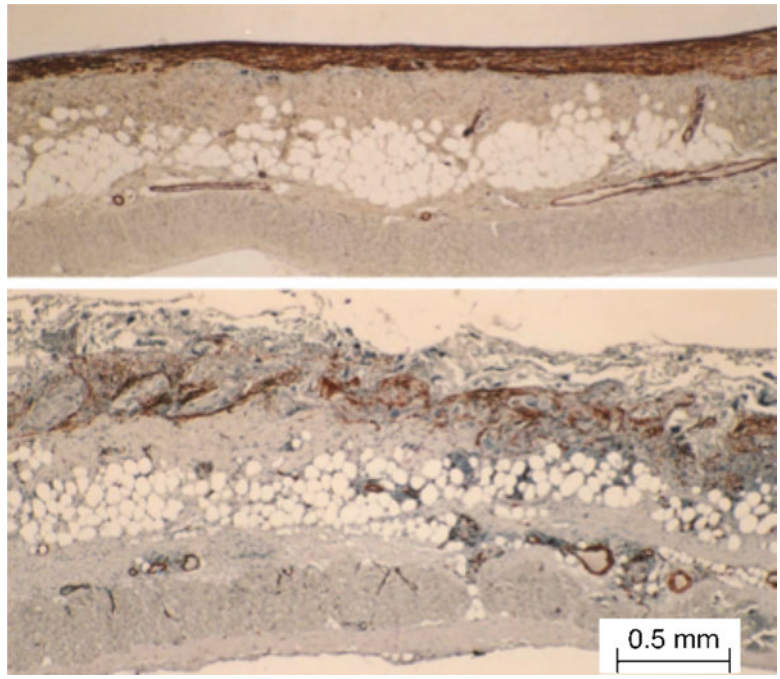

Fig. 9.7 Histological contrast between ungrafted and grafted full-thickness skin wound in the guinea pig. The ungrafted wound is contracting vigorously at day 10 after injury (*above*), whereas the wound grafted with the unseeded dermal regeneration template shows no contraction at the same time following injury (*below*). The tissue sections were stained with an antibody against α-smooth muscle actin, a protein that is synthesized when fibroblasts differentiate to the myofibroblast, the contractile phenotype. In the grafted wound, the myofibroblast density is reduced to approximately 20% of its level in the ungrafted wound; also, the long (contractile) axes of myofibroblasts become randomly oriented in space in the presence of the scaffold [22]. The result is blocking of wound contraction, a prerequisite for induced regeneration (From Yannas IV. Similarities and differences between induced organ regeneration in adults and early foetal regeneration. J R Soc Interface 2005;2:403–417)

is about 2 weeks, again matching roughly the half-life for the healing process in the transected nerve stump [29]. When the scaffold degraded at a slower rate ($t_b \gg 14$ days), the persisting DRT appeared to interfere with synthesis of the regenerate and scar formed around the scaffold. When the half-life of the DRT was significantly lower than the half-life of the contractile response ($t_b \ll 14$ days), the DRT had little effect on blocking contraction or scar synthesis and regeneration was not observed [20].

In summary, DRT dramatically blocks contraction while inducing skin regeneration. Scaffolds that are close in structure to DRT but do not block contraction, do not induce regeneration. There is evidence that DRT prevents recruitment of MFB and formation of oriented structures of MFB, two processes that characterize spontaneous healing in the adult mammal, over the duration of the normal contraction process.

Discussion and Conclusions

The experimental protocols that were used by several independent investigators to induce synthesis of elements of skin and peripheral nerves both in vitro and in vivo were analyzed in an effort to identify the minimal reactants required for organ regeneration. Despite the structural differences between the two organs, the simplest reactants required for induced regeneration of either skin or peripheral nerves were found to be similar. The empirical evidence supports the conclusion

that partial synthesis of either skin or peripheral nerves requires only the implantation of a scaffold with the requisite structure, appropriately seeded with epithelial cells dissociated from the organ of interest. The scaffold should possess a minimal density of specific ligands for contractile cells and an optimal persistence time in the insoluble state [1]. Exogenous reactants utilized widely in many regeneration protocols, notably cytokines and stromal cells (fibroblasts), were redundant. While the experimental evidence derives only from the two organs that have been studied extensively to date in this context, the conclusions reached above may be interpreted as a "trans-organ" approach for future regeneration efforts.

The evidence presented in this chapter shows that severe wounds in several organs in adults heal primarily by contraction, the same mechanism by which skin and peripheral nerves heal in adults. Contraction blocking in skin and in peripheral nerves is associated with induced regeneration. The available data suggest, therefore, the possibility that the mechanism of contraction blocking by scaffolds is similar in these two organs. It now becomes possible to seriously consider the possibility that the adult organism can be enabled to regenerate most of its organs.

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Microvascular Changes in the Diabetic Foot

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Francesco Tecilazich, Thanh Dinh, Antonios Kafanas, and Aristidis Veves

Abstract

Microvascular changes in diabetes are related to the presence of neuropathy and highlighted by increased vascular permeability and impaired autoregulation of blood flow and vascular tone. The functional impairment of the microcirculation has been attributed to deficiencies at the level of the nerve-axon reflex and endothelial cell dysfunction, resulting in diminished expression of endothelial nitric oxide synthetase and poly polymerase. Consequently, there is a diminished hyperemic response, resulting in failure to achieve maximal blood flow following injury. This observed functional ischemia may be a possible mechanism for the poor wound healing in diabetic foot ulcers.

Keywords

Microcirculation • Endothelial dysfunction • Hyperspectral imaging • Near-infrared spectroscopy • Nerve-axon reflex

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Abbreviations

PAS	Periodic acid Schiff
ACh	Acetylcholine
SNP	Sodium nitroprusside
EDRF	Endothelium-derived relaxing factor
EDNO	Endothelial-derived nitric oxide
PKC	Protein kinase C
PARP	Poly ADP-ribose polymerase
AGEs	Advanced glycosylated end products
VPF	Vascular permeability factor
TXA_2	Thromboxane
PGH_2	Prostaglandin
vWF	von Willebrand factor
CAM	Cellular adhesion molecule

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sICAM	Soluble intercellular adhesion molecule
sVCAM	Soluble vascular cell adhesion molecule

Introduction

The notion of "small vessel disease" in diabetic peripheral arterial disease has successfully been dispelled in the last decade through studies demonstrating similar patterns of occlusive disease in both diabetic and nondiabetic limbs at the arteriole level [1, 2]. Since then, numerous studies have refuted the notion of "small vessel disease" and, more importantly, shown that diabetic peripheral arterial disease can be successfully treated with endovascular or surgical bypass techniques [1–4]. Furthermore, vascular reactivity in the vessels of diabetic patients has been shown to be comparable to those of nondiabetic patients based on physiologic studies involving the administration of the vasodilator papaverine into femoro-popliteal bypass grafts [3]. This data, coupled with a vast clinical experience of nearly 3 decades of successful arterial reconstruction in patients with diabetes, has revolutionized the notion of diabetic "small vessel disease" and led researchers to investigate the fundamental changes in diabetic microcirculation [4].

Recent work suggests that while an occlusive disease of the microcirculation does not exist, the microcirculation (predominantly capillaries and arterioles) is impaired in the patient with diabetes. In simplest terms, microvascular dysfunction in diabetes may be described by an increased vascular permeability and impaired autoregulation of blood flow and vascular tone. It is postulated that metabolic derangements as a result of hyperglycemia and insulin resistance work synergistically to create the basis of microvascular dysfunction. Consequently, these metabolic alterations produce functional and structural changes at multiple levels within the arteriolar and capillary levels.

Histology of Skin

Skin receives a rich blood supply from penetrating vessels located in the skeletal muscles and in the connective tissue of the subcutaneous fat septa. These vessels give origin to two distinct microvasculature plexuses, a ramifying arteriole and a venule network. The former, the superficial or subpapillary plexus, lies between the papillary and the reticular dermis, delimitating their boundaries. The latter, the subcutaneous plexus, is instead located between the dermis and the subcutaneous fat. These two parallel oriented plexuses are connected by a rich network of vertical reticular dermal vessels. The small capillary loops extend from the superficial plexus more superficially into the dermal papillae that are closer to the epidermis. The return loop of these small vessels is the so-called postcapillary venule. Other blood vessel plexuses can be also found both in the surrounding dermal tissue in the periphery of the cutaneous appendages and in the hair follicles during the anagen growth phase.

Lymph vessels are distributed around the subpapillary layer. They arise as a blind-ending initial lymphatic vessel (lymphatic capillaries) and extend through the postcapillary lymph vessels to the dermal and subcutaneous lymph vessels. The lymph vessels during their route follow the course of the main blood vessels, veins, and arteries.

Capillaries consist of a single layer of endothelial cells (ECs) and a basement membrane with the adjunction of ascent pericytes. The basement membrane is significantly different in arterial and venous capillaries, since in the former it is solitary and homogenous, and multilayered in the venous system. Arterioles contain, from the lumen outwards, a thin intima, the internal elastic lamina (IEL), the media consisting of one or two layers of smooth muscles, and finally the adventitia composed of loose connective tissue. The ECs in the venules are surrounded by the basement membrane and pericytes, and the ECs in the lymph vessels by elastic fibers and a lax basement membrane.

Skin Innervation

The skin is innervated by efferent nonmyelinated system responsible for the function of cutaneous vasculature and skin appendages and an afferent myelinated and nonmyelinated system responsible for the detection of cutaneous sensation.

The microanatomy of nerve fibers in the skin is similar to that of the vascular plexus. The nerves of the skin derive from musculocutaneous nerves that arise from spinal nerves and follow the main routes of the vascular plexuses.

The autonomic nerves are subdivided according to their function in adrenergic and cholinergic systems. The adrenergic sympathetic nerves are distributed in the arrector pili muscles, blood vessels, and glomus apparatus. The cholinergic nonmyelinated sympathetic nerves innervate the eccrine and apocrine sweat glands. Initially, it was believed that sebaceous glands were not innervated and that the peripheral nervous system had no effect on sebaceous gland activity in normal skin. However, it has been demonstrated that small fibers can be detected around sebaceous glands indicating that sebaceous glands in the skin are controlled through neuronal activity.

The sensory innervation protects the skin from thermal and noxious injuries. These fibers are of type Aδ and C, and their free nerve endings are distributed subepidermally in the papillary dermis and into the epidermis as a 3D network of unmyelinated nerve fibers. These free endings are then connected with special neurogenic structures and individual cells.

The neurogenic specialized structures in the skin include the Merkel cells and the Meissner corpuscles responsible for the detection of light touch. The Pacini corpuscles are found deep in the dermis and the subcutaneous tissue, and are specialized in detecting pressure. The Krause bulbs and the Raffini corpuscles are activated, respectively, by cold and heat. Naked nerve endings in the basal layer of the epidermis are responsible for transmission of pain. Collectively, these structures work as a unique system in a suitable hormonal milieu, where neurotransmitters and various inflammatory factors play an important role to retrieve external stimuli.

Structural Changes in the Microcirculation

Structurally, the most notable changes affecting the microcirculation in diabetes involves thickening of the basement membrane and an observed reduction in the capillary size [5, 6]. However, the density of the skin capillaries does not differ from healthy subjects [7]. These structural changes are more pronounced in the legs, likely being the result of increased hydrostatic pressures [8]. The extent of basement membrane thickening has also been observed to be related to glycemic control, with increased basement thickening in poorly controlled diabetic patients [9].

In the diabetic foot, basement membrane thickening has been demonstrated in the muscle capillaries [10]. The sequence of events leading to basement membrane thickening begins with the increased hydrostatic pressure and shear force in the microcirculation. This is thought to evoke an injury response on the part of the microvascular endothelium with subsequent release of extravascular matrix proteins. Subsequently, thickening of the basement membrane with arteriolar hyalinosis occurs [11].

Because changes in the basement membrane can affect numerous cellular functions, such as vascular permeability, cellular adhesion, proliferation, differentiation, and gene expression, alterations in its components may cause vascular dysfunctions. Thickening of the basement membrane impairs the normal exchange of nutrients and activates leukocyte migration between the capillary and interstitium. Furthermore, the elastic properties of the capillary vessel walls are diminished, limiting their ability to vasodilate [12]. As a result, the normal hyperemic response to injury is impaired, limiting the compensatory arteriolar dilatation in response to local injury, resulting in a reduced hyperemic response [13]. It is important to note that basement membrane thickening does not appear to lead to narrowing of the capillary lumen; instead, arteriolar blood flow is observed at normal levels or even increased despite these changes [14].

Functional Changes in the Microcirculation

The observed failure of the microcirculation to vasodilate in response to injury has been described as a functional ischemia and has been demonstrated to be a result of a number of factors at play in the diabetic patient's

microcirculation. Alteration in the microcirculation of the foot has been postulated to be an important factor in the poor wound healing associated with chronic diabetic foot ulcerations. Recent work has investigated these changes, with specific emphasis placed on the changes in the diabetic foot microcirculation, nerve function, and muscle metabolism.

Functional changes in the microcirculation include reduced elasticity of capillaries (and thereby vasodilating capacity) and impaired cellular migration and nutrient exchanges. These abnormalities are thought to be due to endothelial dysfunction, smooth muscle cell dysfunction, and impairment of the nerve-axon reflex. While the exact mechanisms of endothelial dysfunction and smooth muscle cell dysfunction remain unknown, measurements in the diabetic neuropathic foot have shown that the neurovascular response is impaired, leading to a significant reduction in blood flow under conditions of stress.

The functional impairment of the microcirculation has been attributed to reduced expression of endothelial nitric oxide (NO) synthetase and poly polymerase [15, 16]. Furthermore, expression of endothelial nitric oxide synthetase is reduced in peripheral neuropathy, suggesting a relationship between neuropathy and endothelial dysfunction. Under conditions of stress such as pain and trauma, the C fibers secrete peptides, such as Substance P, Neuropeptide Y, Neurotensin, and others, that exert vasodilation and increase vessel permeability. This represents a protective mechanism, and it has been shown to be impaired in the diabetic patients with and without neuropathy [17–19], with the largest reduction observed in neuropathic feet (Fig 10.1). This characteristic impairment at the foot level can also be considered as a functional ischemia and it may be another possible mechanism that explains poor wound healing in DFU.

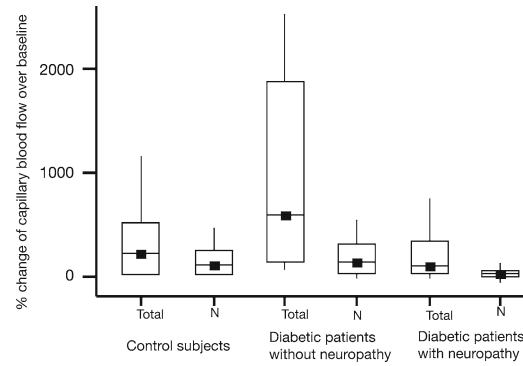

Fig. 10.1 Total and neurovascular (N) change in skin blood flow in response to acetylcholine at the foot level. The median, first quartile, and third quartile and the range are shown. The total response is significantly lower in neuropathic diabetic patients than it is in control subjects and diabetic patients without neuropathy ($p<0.01$). The percentage contribution of neurovascular response to the total response is also significantly lower in neuropathic diabetic patients than in control subjects and diabetic patients without neuropathy ($p<0.01$) (reprinted with permission from Parkhouse and Le Quesne [19])

Functional Changes in the Diabetic Foot

The resting total skin microcirculation in the diabetic foot is comparable to that of the nondiabetic foot, when peripheral neuropathy is absent. However, when neuropathy is present, the capillary blood flow has been shown to be reduced [16, 20]. This may indicate a maldistribution of blood flow to the skin, with a resultant functional ischemia. As previously mentioned, the hyperemic response is impaired in the diabetic microcirculation, thereby failing to achieve maximal blood flow following injury.

Functional changes in the microcirculation appear to impact the ability of precapillary arterioles and capillaries to vasodilate in periods of stress or injury. Clinical examination of the neuropathic diabetic foot with an ulcer may demonstrate a warm foot with palpable pulses and distended veins; paradoxically, however, this foot may be functionally ischemic. In fact, diabetic autonomic neuropathy with sympathetic denervation may lead to the opening of subpapillary arteriovenous shunts with a resultant augmentation of blood flow maldistribution between the nutritional capillaries and the subpapillary vessels [7, 21]. Therefore, although there appears to be no reduction in foot vascularization, the skin microcirculation will be dramatically reduced [22–24]. Ultimately, arteriovenous shunting further aggravates the functionally ischemic foot, as evidenced by studies using venous occlusion

plethysmography, Doppler sonography, and venous oxygen tension measurements [25].

Vasodilation

The endothelium is a diaphanous cellular monolayer that forms the inner layer lining of blood vessels. By virtue of its direct contact with circulating blood, endothelial cells serve as important autocrine and paracrine regulators of vascular function, and provide a critical interface between the elements of blood and tissues. Vascular smooth muscle cells (VSMCs) are small, spindle-shaped mononucleated cells that surround the endothelial monolayer with a variable number of layers depending on vessel location and size: large (elastic) arteries contain many layers of VSMCs alternated with sheets of elastic laminae; precapillary (resistance) arteries may instead have only a single VSMC layer [26]. The IEL lies in between the smooth muscle cell and endothelium layers [27]. Direct communication among cells of the artery wall is enabled by gap junctions. These contacts allow the passage of small molecules and electrical current, and are present both among same cell types (EC–EC and VSMC–VSMC), called homo gap junctions, and in between different cell types (EC–VSMC), known as hetero or myoendothelial gap junctions (MEGJs). MEGJs comprise an EC projection that reaches a VSMC through an IEL perforation [27]. Transmission of membrane hyperpolarization through gap junctions is the key factor of the phenomenon called "spreading vasodilation" that allows diffusion of vasodilation from stimulated to adjacent vessel segments.

In 1980, Furchgott and Zawadzki discovered that arterial vasodilation was dependent on an intact endothelium and its release of a substance they called endothelium-derived relaxing factor (EDRF), which causes arterial smooth muscle relaxation in response to ACh and other vasodilators [28]. Later, this molecule was identified as endothelial-derived nitric oxide (EDNO), a gas that is synthesized from the precursor L-arginine in a reaction catalyzed by nitric oxide synthase. After its secretion from the endothelium, NO diffuses to the adjacent smooth muscle cells and induces VSMC relaxation through the activation of the cyclic GMP and the hyperpolarization of the muscle cell membrane. The activation of cyclic GMP in fact induces the activation of VSMC guanylate cyclase, with subsequent elevation of cGMP levels which in turn leads to a reduction in intracellular Ca^{++} resulting in smooth muscle relaxation and thereby vasodilation.

As previously stated, ECs synthesize and release both relaxing factors, such as NO and prostacyclin (PGI2), and contracting factors, such as endothelin-1 (ET-1), prostaglandins, and angiotensin II (ANG-II). NO is the main vasodilatatory mediator; however, other vasodilating agents exist, such as PGI2, a cyclooxygenase-dependent metabolite of arachidonic acid [29]. Among these, increased evidence for endothelium-derived hyperpolarizing factor (EDHF) has accumulated in the last years. The name originates by the observation that this vasodilating mechanism is abolished by potassium channel (K^+-channel) blockers or by depolarizing concentration of K^+. Direct hyperpolarization of the VSMC membrane is instead achieved through nitrosylation of the K-ATP channel and, therefore, an increase of the pump's activity [30]; this mechanism is extremely important since it counteracts the effects of vasoconstrictive agents.

Under physiological circumstances, mechanisms leading to vasodilatation and vasoconstriction are balanced, so vascular tone and permeability and balance between coagulation and fibrinolysis are finely regulated. Meanwhile, in case of endothelial dysfunction, this balance is altered predisposing the onset and progression of atherosclerosis. Endothelial dysfunction is associated with decreased NO availability, either through loss of NO production or loss of NO biological activity [31]. The significance of endothelial dysfunction on the micro- and macrocirculation and the variety of proposed mechanisms affecting normal function are discussed in further detail.

Endothelium-Dependent Vasodilation

The majority of studies agree that the endothelium-dependent vasodilation in the large vessels

is impaired in diabetes, irrespective of the presence or absence of long-term complications [32–36]. Initial studies of endothelium-dependent vasodilation used venous occlusion plethysmography, while subsequent studies employed flow-mediated vasodilation, a noninvasive technique. Through these techniques, endothelium-dependent vasodilation has been shown to be impaired in adolescents with type 1 diabetes, a population that is generally spared from the micro- and macrovascular complications of diabetes [37]. This finding suggests that endothelial dysfunction is present before the development of these vascular complications and may play an important role in their development. Finally, endothelial function in type 1 diabetes has been shown to be associated with total cholesterol, red cell folate, blood glucose levels, and duration of diabetes [38–40].

In the last decade, extensive research effort has focused on the relationship of type 2 diabetes and vascular disease. Thus, it is currently well established that endothelium-dependent vasodilation is impaired in both the micro- and macrocirculation in type 2 diabetes. Furthermore, there is almost universal agreement that changes in the endothelial function precede the development of diabetes and are already present in the prediabetic stage. It is also of interest that endothelial dysfunction is associated with insulin resistance in nondiabetic subjects, suggesting a cause–effect in the relationship of these two conditions [36].

A study conducted in our unit found that the vasodilatatory response to ACh was reduced in patients with diabetes complicated by neuropathy alone, neuropathy and vascular disease, and patients with Charcot neuroarthropathy, meanwhile no difference was found between patients with diabetes not complicated by neuropathy and the healthy controls (Fig. 10.2). We also found that the vasodilatory response was not diminished in subjects with neuropathy and vascular disease compared to subjects with neuropathy alone. All together, this data suggested for the first time the fundamental role played by the peripheral nerval system in regulating microcirculation and in the pathogenesis of diabetic foot ulceration [16].

Impairment in the microcirculation was also found to be present in the absence of large vessel disease. These findings implied that the main reason for reduced microvascular reactivity was the presence of neuropathy, as indicated by the fact that no other abnormalities were found in the non-neuropathic diabetic patients. Further support for this claim is provided by the findings that the coexistence of neuropathy and vascular disease did not result in a greater decrease in endothelium-dependent vasodilation than that due to neuropathy alone.

Endothelium-Independent Vasodilation

VSMCs are to be considered "the muscle behind vascular biology," since they represent the final effectors of the vasodilating process. Vasodilation is determined by relaxation of VSMCs, mainly achieved through the NO activation of soluble guanylate cyclase with subsequent formation of cyclic GMP that in turn activates protein kinase G, causing phosphorylation of myosin light-chain phosphatase and, therefore, inactivation of myosin light-chain kinase that ultimately leads to the dephosphorylation of the myosin light chain. EDHF determines vasodilation by transmitting hyperpolarization from endothelial cell to VSMCs through gap junctions and/or the release of diffusible factors. Hyperpolarization of the endothelium depends on the activation of the intermediate- and small-conductance calcium-activated potassium channels (IKCa and SKCa, respectively) present on the surface of the ECs.

Data on endothelium-independent vasodilation function in complicated and noncomplicated diabetes is controversial [41–45]. Recent investigation has suggested that endothelium-independent vasodilation is decreased in patients with diabetes [16] (Fig. 10.2). Using laser Doppler imaging, measurements of vasodilatory response to iontopheresis of sodium nitroprusside on VSMC function have been shown to be significantly reduced in diabetic patients with vascular disease, suggesting that the endothelium-independent response may be spared. Since ACh stimulates the production of nitric oxide, it was surmised that an impaired nitric oxide production was responsible for the impaired vasodilatory response observed.

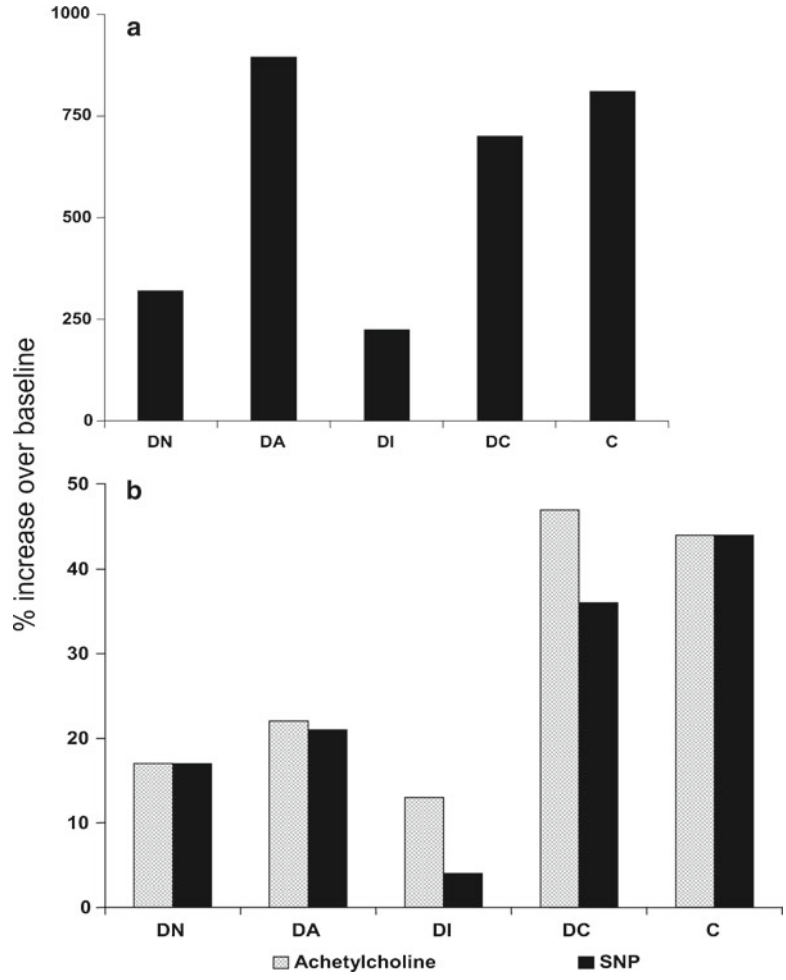

Fig. 10.2 (**a**) The maximal hyperemic response to heating of foot skin at 44°C for at least 20 min (expressed as the percentage of increase over baseline flow measured by a single-point laser probe) is reduced in the diabetic with neuropathy (DN) and in diabetic patients with neuropathy and peripheral vascular disease (DI) when compared with diabetic patients with Charcot arthropathy (DA), diabetic patients without complications (DC), and normal control subjects (C) ($p < 0.001$). (**b**) The response to iontophoresis of acetylcholine and sodium nitroprusside (SNP) (expressed as the percentage of increase over baseline flow measured by laser scanner imager). The response to acetylcholine is equally reduced in the DN, DI, and DA groups when compared with the DC and C groups ($p < 0.001$). The response to SNP was more pronounced in the DI group and also reduced in the DN and DA groups compared with the DC and C groups ($p < 0.001$) [26]

Nerve-Axon Reflex

Nerve dysfunction contributes to the diminished vasodilatatory response observed in diabetes. Under normal conditions, the ability to increase blood flow to the skin depends on the existence of an intact neurogenic vascular response. This protective hyperemic response, also known as Lewis' triple flare response or the nerve-axon reflex vasodilation (NARVV), begins with the stimulation of C-nociceptive nerve fibers, leading to antidromic stimulation of the adjacent C fibers (Fig. 10.3). The activated C fibers then secrete neuropepetides, such as substance P,

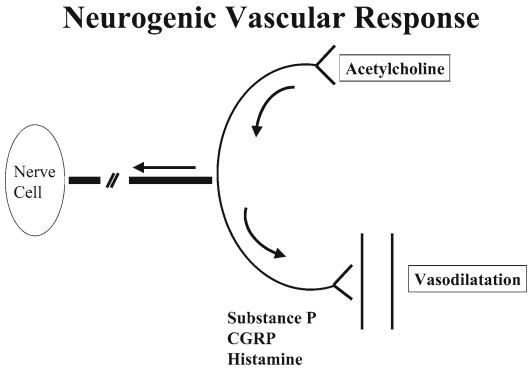

Fig. 10.3 Stimulation of the C-nociceptive nerve fibers leads to antidromic stimulation of the adjacent C fibers, which secrete substance P, calcitonin gene-related peptide (CGRP), and histamine that cause vasodilatation and increased blood flow

calcitonin gene-related peptide, and histamine, causing vasodilation and increased blood flow to the injured tissues. Typically, this response is equal to one-third of the maximal vasodilatory capacity and depends on the existence of an intact neurogenic vascular response.

Measurements in the diabetic neuropathic foot have shown that this neurovascular response is impaired, leading to a significant reduction in blood flow under conditions of stress. It has been postulated that the observed reduction in the NARV in diabetic neuropathy is related to both impaired C-nociceptive fiber function and impaired ability of the microvasculature to respond to vasomodulators secreted by these fibers [46]. Evidence for this vasodilatatory impairment related to the presence of diabetic neuropathy is provided by studies in our lab that used the previously described single-point laser probe technique to evaluate the NARV response. In patients with neuropathy alone, neuropathy and peripheral vascular disease, and Charcot arthropathy the iontophoretic response to ACh was significantly reduced when compared to patients with not complicated diabetes and to healthy subjects. This phenomenon was apparent in the skin adjacent to ACh, but not in areas in direct contact with it [47].

The impairment in axon-related vascular reactivity is believed to further aggravate the diabetic microcirculatory abnormalities, determining a vicious cycle [16]. Thus, in the diabetic neuropathic foot, the involvement of the C-nociceptive fibers does not only lead to the well-known altered pain perception, but also to impaired vasodilation under stresses, such as infection and injury (i.e., functional ischemia).

Mechanisms of Endothelial Dysfunction

Endothelial dysfunction is expressed in increased interactions with leukocytes, smooth muscle growth, vasoconstriction, impaired coagulation, vascular inflammation, thrombosis, and atherosclerosis. There is substantial evidence that endothelial function is abnormal in patients with both type 1 and type 2 diabetes mellitus [34, 35]. The causes of endothelial dysfunction have been postulated to include hyperglycemia, insulin resistance, and inflammation as possible mediators of abnormal endothelium-dependent responses.

Endothelial Dysfunction and Hyperglycemia

A variety of mechanisms have been proposed for endothelial dysfunction in hyperglycemia, mainly through the induction of oxidative stress. The main mechanisms involved in this process include the activation of protein kinase C (PKC), increased vasoconstrictor protanoids synthesis, reduction of the Na^+-K^+ ATPase activity, poly (ADP-ribose) polymerase (PARP) activation, production of oxygen-derived free radicals, increased synthesis of ET-1, induction of the polyol pathway, and generation of advanced glycosylated end products (AGEs).

1. PKC

   PKCs include a superfamily of cytoplasmic serine/threonine kinases isoenzymes. Increased activation of PKC, a key player in intercellular signal transduction for hormone and cytokines, may be the result of hyperglycemia and elevated fatty acids present in T2DM [48]. PKCs participate in vascular cell signal transduction and mediate diverse signaling, including oxidant, inflammatory, mitogenic, and angiogenic effects, in diabetic

vascular tissues that may promote atherosclerotic CVD [49, 50]. PKC activation leads to increased production of extracellular matrix and cytokines; it enhances contractility, permeability, and vascular cell proliferation; induces the activation of cytosolic phospholipase A2; inhibits the activity of Na^+-K^+-ATPase; and regulates neovascularization via the expression of growth factors, such as VEGF/vascular permeability factor (VPF) [51]. Ruboxistaurin (RBX) mesylate is a PKC inhibitor that specifically inhibits PKC-β overactivation. RBX has shown to improve neural function in diabetic animals [52]; but in a double-masked randomized clinical trial conducted in patients with DPN, RBX failed to achieve the primary end point, that is, the improvement of quantitative sensory testing for vibration detection threshold among all symptomatic patients. However, the study showed that treatment with RBX at the dosage of 64 mg, compared to placebo, determined a significant improvement in the neuropathy total symptoms score-6 (NTSS-6) at 6 and 12 months, in the group classified at baseline with clinically significant sensorial neuropathy and treated with RBX [53].

2. Vasoconstrictor protanoids synthesis
   Experimental studies in diabetic animals have also indicated that abnormal endothelial production of vasoconstrictor prostanoids may be a cause of endothelial cell dysfunction. Increased levels of thromboxane (TXA_2) and prostaglandin (PGH_2) have been isolated from segments of diabetic vascular tissue. In human studies, however, the role of vasoconstrictor prostanoids is less clear. Flow-dependent vasodilation in healthy subjects, which may be used as an index of endothelial function, is unaffected by aspirin, thus demonstrating that it is entirely mediated by EDNO and independent of vasoactive prostanoids [54].
3. PARP
   Recent work has also shed light on the role of PARP in endothelial function [15]. PARP is a nuclear enzyme that responds to oxidative DNA damage by activating an inefficient cellular metabolic cycle, often leading to cell necrosis. PARP's activation, besides being related to endothelial dysfunction in patients with diabetes, has been observed also in healthy patients at risk for developing diabetes [15]. It was observed that the activation of PARP was associated with changes in the vascular reactivity of the skin microcirculation, supporting the hypothesis that PARP activation contributes to changes in microvascular reactivity. These findings overall suggest that changes in the microcirculation due to PARP activation may begin in the prediabetic state.
4. Oxygen-derived free radicals
   It has recently been proposed that oxidative stress contributes to the development of diabetic vascular complications through an increased production of oxygen-derived free radicals. This increased production in diabetes directly inactivates endothelium-derived nitric oxide, thereby reducing the bioavailability of EDNO [55]. In animal models, endothelium-derived free radicals impaired EDNO-mediated vasodilation. In human studies, administration of vitamin E (400 IU/day), a potent free radical scavenger, had no apparent effect on cardiovascular outcomes in patients with diabetes with complications [56]. However, early studies showed that high-dose vitamin E (1,800 IU/day) normalized hemodynamic abnormalities, suggesting that administration of an antioxidant may reduce the risks of diabetic vascular complications [57]. Later studies involving long-term high-dose vitamin E found no beneficial effects on endothelial function or left ventricular function in type 1 and type 2 diabetic patients [58]. Furthermore, high-dosage vitamin E was also associated with worsening in some vascular reactivity measurements when compared with control subjects.
5. ET-1
   Hyperglycemia, oxidative stress, and AGEs induce the synthesis of ET-1, a potent vasoconstrictor, through the activation of NF-kB [59]. The upregulation of ET-1 seems to be a consequence of the NO–Ang II imbalance; however, the exact mechanism by which hyperglycemia induces its increase is still not

completely understood. Another possible pathway responsible for the increase of ET-1 is the PKC-mediated induction of the endothelin-converting enzyme (ECE)-1, which catalyzes the conversion of the inactive ET-1 to the active form [60].

6. Polyol pathway
   In the presence of hyperglycemia, glucose enters the polyol pathway. In this pathway, aldode-reductase (AR), using NADPH as a cofactor, catalyzes the reduction of glucose to sorbitol, an organic osmolyte. Subsequently, sorbitol dehydrogenase oxidizes sorbitol to fructose, with production of NADH from NAD^+. Since NADPH is fundamental for synthesizing nitric oxide and glutathione, the polyol pathway activation results in increased concentrations of sorbitol (with subsequent osmotic stress), fructose (which is ten times more potent glycation agent than glucose), and reactive oxygen species, and in decreased concentrations of NO and glutathione [61]. The role for AR in the pathogenesis of diabetic chronic complications has been extensively reviewed [62]. New evidence has recently emerged on the increased activity of AR during hyperglycemia- and diabetes-induced oxidative–nitrosative stress [61] and the downstream activation of mitogen-activated protein kinase (MAPK) [63], PARP [64], and NF-kB [63].

   The accumulation of sorbitol causes the depletion of other osmolytes, like myo-inositol and taurine [65]. The depletion of myo-inositol impairs the phosphoinositide metabolism and, through this, is in part responsible for the reduction in Na^+/K^+-ATPase activity. The proposed mechanism by which myo-inositol affects Na^+/K^+-ATPase function is through the impaired activation of neural PKC caused by diminished phosphoinositide-derived diacylglycerols [66]. The Na^+-K^+-ATPase is involved in the maintenance of cellular integrity and functions of contractility, growth, and differentiation. Therefore, impairment of this mechanism can lead to vascular dysfunction and the early reversible nerve conduction defect in experimental diabetes [67].

   In the last 30 years, over 32 randomized controlled trials have tested the efficacy of AR inhibitors (ARIs), such as ranirestat and epalrestat, in the treatment of diabetic neuropathy. A meta-analysis involving 879 ARI-treated and 909 control (placebo or no treatment) participants showed no overall significant difference in the treatment of diabetic polyneuropathy between the groups [68].

7. AGEs
   AGEs result from a nonenzymatic reaction when proteins are exposed to hyperglycemic environments. The resultant Schiff bases can be rearranged to form Amadori products, AGEs, and reactive oxygen species. Increased AGE levels have been found in patients with diabetes and may contribute to the increased vascular permeability of diabetes, since blockade of a specific receptor for AGE reverses diabetes-mediated vascular hyperpermeability [69]. Furthermore, the generated reactive oxygen species have been shown to cause severe disturbances in the regulation of coronary flow and cellular hemostasis, leading to the severe macrovascular lesions typically observed in diabetic patients after more than 10 years of disease [70]. Interestingly, inhibition of reactive oxygen species also prevents the generation of AGE products, suggesting that the autoxidative process plays an important role in the complex reaction cascade leading to AGE.

Endothelial Dysfunction and Insulin Resistance

Besides its anabolic action, insulin also exerts a hemodynamic action that results in peripheral vasodilation and capillary recruitment. Insulin mediates vasodilation through modulating the synthesis and release of NO [47, 71]. Insulin's stimulation of NO is mediated by the activation of signaling pathways involving the recruitment of phosphoinositide-3 (PI-3) kinase that leads to the phosphorylation of eNOS. Interestingly, it has been proposed that as much as 25% of insulin's stimulatory effect on muscle glucose uptake is related to its hemodynamic actions [72]. By contact with the endothelial barrier, insulin

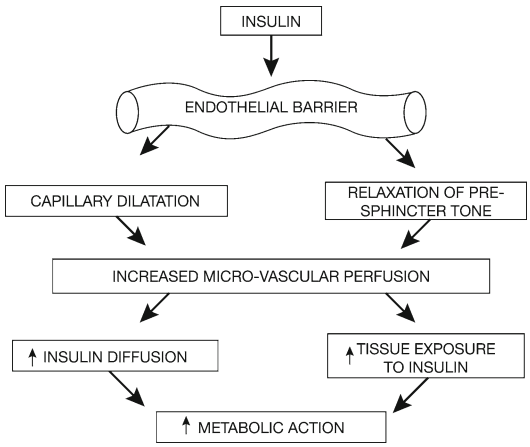

Fig. 10.4 Hemodynamic and metabolic actions of insulin. Insulin stimulates an increase in recruitment of microvessels, expansion of the capillary network, and perfusion of the microcirculation via relaxation of the precapillary sphincter tone and dilatation of the capillaries. Insulin, thereby, diffuses into the interstitium more readily and the target tissues are exposed to high insulin concentrations. This determines ultimately an increased insulin-mediated glucose metabolism (reproduced with permission from Cersosimo and DeFronzo [73])

determines dilation of the capillaries and relaxation of the presphincter. In this way, insulin's metabolic action is enhanced, both by recruiting new capillary beds and redirecting the capillary blood flow more toward insulin-sensitive tissues (muscle and adipocytes) and away from insulin-independent tissues (bone and skin) [73] (Fig 10.4).

The bidirectional link between hyperinsulinemia and endothelial dysfunction is well established. On one hand, the exposure of vascular endothelium to hypertriglyceridemia and elevated small dense LDL cholesterol particles, typical of insulin resistance states, is accompanied by reduced NO availability [74]. On the other hand, endothelial dysfunction contributes to impaired insulin action by altering the transcapillary passage of insulin to target tissues. Although the molecular mechanisms determining the metabolic and vascular abnormalities associated with the insulin resistance state have yet to be entirely elucidated, the impaired NO production clearly appears to play a pivotal role.

Endothelial Dysfunction and Inflammation

The origins of heightened inflammatory activity in type 1 and type 2 diabetes are very different. In type 1 diabetes, even though the inflammatory process plays a greater role in the long-term progression of disease, the onset is the consequence of an islet inflammation that is thought to be a local phenomenon triggered by a focal autoimmune activation. In T2DM, the activation of inflammation results from systemic etiologic factors, such as central obesity and insulin resistance. In both T1DM and T2DM, an important role in the maintenance and exacerbation of the inflammatory reaction is played by hypertension and dyslipidemia in concert with hyperglycemia.

An early feature of inflammation is the release of chemokines, such as C-reactive protein (CRP), fibrinogen, interleukin-6 (IL-6), interleukin-1 (IL-1), TNFα, and monocyte chemoattractant protein (MCP)-1. These factors promote the expression of interstitial and vascular cellular adhesion molecules, like ICAM-1, VCAM-1, and E-selectin, and attract monocytes and immunocytes [75]. Inflammatory cytokines increase the vascular permeability, change the vasoregulatory responses, and increase the adhesion of leukocyte to endothelium. Furthermore, inflammatory cytokines facilitate thrombus formation by inducing procoagulant activity, inhibiting anticoagulant pathways and impairing fibrinolysis by increasing the expression of plasminogen activator inhibitor (PAI)-1 and tissue factor, through platelet activation and acute-phase reactions that increase the circulating levels of coagulation factors, such as fibrinogen and factor VIII [75].

Biochemical Markers of Endothelial Dysfunction

When the endothelium has been injured, a number of vasoactive substances are produced in response. As a result, these biochemical markers, such as von Willebrand factor (vWF) and cellular

adhesion molecules (CAMs), have been employed to evaluate endothelial dysfunction. vWf, a multimeric glycoprotein mainly synthesized by endothelial cells, is involved in platelet adhesion and aggregation and acts as the carrier of coagulation factor VIII in plasma. Increased levels of vWf, reflecting activation of or damage to endothelial cells, have been described in association with atherosclerosis and diabetes. Initial studies in patients with diabetes have demonstrated increased plasma levels of vWF [76]. Furthermore, these elevations preceded the development of albuminuria and peripheral nerve dysfunction. Therefore, it has been suggested that vWF could be used as a predictive indicator of vascular complications.

CAMs are expressed on endothelial cells in response to inflammation and facilitate the adhesion of circulating leukocytes to their surface. Increased levels of soluble intercellular adhesion molecule (sICAM) in healthy individuals have been linked with a higher risk of future cardiovascular complications [77]. Furthermore, both sICAM and soluble vascular cell adhesion molecule (sVCAM) levels have been reported to be higher in patients with diabetes and, in some instances, individuals with impaired glucose tolerance (IGT) [78, 79].

In vitro studies of sICAM and sVCAM demonstrated that these biochemical markers were expressed by endothelial cells following a short period of incubation in high glucose conditions [80], lending support that hyperglycemia plays a role in activation of these molecules. Furthermore, a direct correlation has been detected between VCAM-1 and VEGF, suggesting that cellular adhesion and neovascularization may be linked processes [81].

Methods of Evaluating the Microcirculation of the Feet

Recent technological advances over the last decade have enabled us to evaluate the functional microcirculation of the feet. Methods, such as Laser Doppler flowmetry, flow-video microscopy, cannulation measurements of capillary pressure, and transcutaneous oxygen tension measurements, have all been used. The most commonly used technique, and the one used in our lab, for evaluating blood flow in the skin remains Laser Doppler flowmetry.

Laser Doppler Flowmetry

This method is considered the most widely accepted technique for evaluating capillary blood flow in the skin microcirculation based on its ease of use and reproducibility. This method uses a red laser light that is transmitted to the skin through a fiber-optic cable. The frequency shift of light backscattered from the moving red blood cells beneath the probe tip is used to give a measure of the superficial microvascular perfusion [16]. The method of laser scanning also uses the technique of iontophoresis to evaluate microvascular reactivity. More specifically, a device consisting of two chambers that accommodate two single-point laser probes is applied to the skin. A small quantity (<1 mL) of the vasoactive substance is placed in the chamber while a second nonactive electrode is placed 10–15 cm away from the chamber. A constant current of 200 μA is applied, creating movement of the solution toward the skin, causing vasodilation. Iontophoresis of ACh chloride measures the endothelium-dependent vasodilation, while sodium nitroprusside measures the endothelium-independent vasodilation.

There are two types of laser probes available for use with this method: a single-point laser probe or a real-time laser scanner. The single-point laser probe measures the microvascular blood flow at a single point in the skin, and has been used for evaluating the hyperemic response to a heat stimulus or for evaluating the NARV-related hyperemic response. In conjunction with the technique of iontophoresis and the addition of a second probe, the single-point laser probe method can be used to assess the integrity of the NARV. In the two single-point laser probe technique, the first probe is exposed to ACh in order to measure the blood flow to a specified area of skin. The second probe is situated in close proximity (5 mm) to the first probe, and consequently measures the indirect effect of the iontophoresed ACh. The indirect effect of the ACh results from stimula-

tion of the C-nociceptive nerve fibers and, therefore, the NARV hyperemic response [82, 83]. Following iontophoresis of the vasoactive substance, the adhesive device is removed and the area of skin is scanned with a laser Doppler scanner. Measurement of the hyperemic response to a heat stimulus is performed by first taking baseline blood flow measurements. Next, the skin is heated to 44°C for 20 min using a small brass heater or, in our experience, maintaining the ambient room temperature at this level. Following this, the maximum blood flow is determined by the magnitude of blood flow change in response to heat.

The laser Doppler perfusion imager uses 1-mW helium–neon laser beam of 633-nm wavelength to sequentially scan the area of skin. Increased blood flow at the skin level is recorded by the scanner and expressed in volts. This technique has been validated against direct measurements of the capillary flow velocity with consistent measurements achieved. In clinical settings, measurements of endothelial function with laser Doppler in conjunction with iontopheresis of ACh yielded consistent results in patients with diabetes and coronary heart disease.

Flow-Video Microscopy

Flow-video microscopy enables measurements of capillary blood flow along with such parameters as average flow velocity, peak postocclusive hyperemic flow velocity, and response to other physiologic maneuvers. With the use of an image-shearing monitor, the capillary red cell column width is calculated. This is performed by lighting mercury vapor onto skin that has previously been brushed with a thin film of oil or varnish in order to limit the scattering of light. The image of the moving blood elements can then be recorded with a low-light-sensitive video system [84].

More recently, a digitized system has been developed that is capable of recording continuous capillary blood flow. Measurements are then calculated through an integrated software program. However, this method may underestimate the true capillary lumen due to the unvisualized marginal plasma layer.

Capillary Pressure Measurements

The measurement of capillary pressure involves direct cannulation of a single vessel. Following cannulation of the vessel, the transmitted pressure can be measured manometrically or through use of an electronic device. This invasive technique is capable of detecting small changes in the capillary pressure as low as 1–2 mmHg. Additionally, it has the added benefit of being able to measure the capillary pressure continuously. However, the procedure can be complex and may require significant expertise.

Transcutaneous Oxygen Tension Measurements

The measurement of oxygen transcutaneously ($TcPO_2$) can be performed based on the fact that oxygen is capable of diffusing throughout the body tissue and skin. While the rate of diffusion is very low at normal surface body temperature, application of heat to a localized area can sufficiently enhance the flow of oxygen through the dermis to allow for noninvasive measurement of the capillary oxygen level. However, these measurements suffer from inconsistency as they can be inaccurate as they appear to fluctuate with the skin temperature and room temperature. As a result of this variability, the clinical use of $TcPO_2$ has been restricted [85, 86].

Latest Developments

Hyperspectral Imaging

Hyperspectral imaging (MHSI) emerged as a method of "imaging spectroscopy" that provides spatial measurements of the skin's oxy- and deoxyhemoglobin levels [87] and quantifies the skin oxygenation by combining the chemical specificity of spectroscopy with the spatial resolution of imaging. A spectrum of reflected light is acquired for each pixel in a region, and each spectrum can be subjected to standard analysis. This allows the creation of an image based on the chemistry of the region of interest (ROI).

MHSI has been used for decades in a wide variety of applications ranging from geological and agricultural to military and industrial, and recently

has begun to be applied also to biomedicine [19]. Using spatially resolved oxygen saturation maps, MHSI can predict tissue viability following plastic surgery [88], differentiate tumor from normal tissue, assess local tissue viability following partial thickness burns [85, 86], and determine the local skin manifestations of larger systemic problems, such as shock [87]. These capabilities are highly advantageous in the evaluation of small wound regions, where the detection of subtle microcirculatory differences is necessary.

In the research arena, MHSI has been used to identify differences of the skin oxygenation between healthy control subjects and diabetic patients with and without neuropathy. MHSI has shown that hemoglobin saturation is reduced in the skin of patients with diabetes and that this impairment is accentuated in the presence of neuropathy in the foot, suggesting that microcirculatory changes could play a major role in the development of neuropathy. Furthermore, these changes could underlie the development of foot ulceration and, more importantly, preclude the healing of existing ulcers [89, 90].

In a follow-up study, the ability of this technique to predict diabetic foot ulceration healing was examined and the progress of foot ulcers was tracked over a period of 6 months [90]. The results of this study provided the proof of concept that MHSI, evaluating wound oxygenation and its relationship to wound healing, could satisfactorily predict ulcer healing and therefore has the capability to assist in the management of DFU [90].

Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIR) is a spectroscopic method which uses the near-infrared region of the electromagnetic spectrum. NIR can typically penetrate much farther into a sample than mid infrared radiation and can be used to monitor changes in vascularization, hemoglobin concentration, and collagen concentration, and can therefore be used to obtain a measure of the optical absorption and optical scattering properties of probed tissue. The optical properties of tissues at visible and near-infrared wavelengths are determined mostly by the levels of oxygenated and deoxygenated hemoglobin in the probes tissue. The sensibility and specificity of NIR in evaluating changes in muscle blood flow are currently under investigation. Changes in blood flow at resting conditions and during exercise may suggest a relationship between lower extremity dysfunction with changes in both the micro- and macrocirculation and the development of peripheral neuropathy.

Conclusion

In conclusion, while an occlusive disease of the microcirculation does not exist, functional impairment of the microcirculation in diabetes may contribute to secondary complications, such as foot infections and ulcerations. Microcirculation to the diabetic foot suffers both structural and functional derangements. Nerve-axon-related microvascular reactivity is clearly impaired in the diabetic population and there is a growing belief that both the failure of the vessels to dilate and the impairment of the nerve-axon reflex are major causes for impaired wound healing in diabetic patients. Further studies are necessary to clarify the precise etiology of observed endothelial dysfunction in diabetic and neuropathic patients and to identify the possible potential therapeutic interventions to prevent or retard its progression.

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Biomechanics of the Diabetic Foot: The Road to Foot Ulceration

11

Carine van Schie and F.J. Slim

Abstract

Diabetic peripheral neuropathy can cause changes in foot structures and function as well as gait abnormalities, which subsequently can lead to abnormal mechanical loading of the foot. Foot deformities, such as prominent MTHs, clawed toes and Charcot neuroarthropathy, are strongly associated with and predictive of increased plantar pressure and foot ulceration. Limited joint mobility of the foot and ankle has also been suggested to increase foot pressure and to be related to foot ulceration. Additionally, changes in quantity and quality of plantar subcutaneous fat cushioning are indicators of abnormal foot loading during walking, thereby causing high plantar foot pressure. Excessive and/or repetitive pressure applied to the plantar surface of the foot appears to be the main causative factor for development of skin breakdown. However, often, it is the combination of footwear characteristics, lifestyle factors, soft tissue characteristics, plantar foot pressures and level of physical activity that contribute to the development of foot ulceration.

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Foot Function

One of the principal functions of the foot is its shock-absorbing capability during heel strike and its adaptation to the uneven surface of the ground during gait. In this function, the subtalar joint plays a basic role. The subtalar joint allows motion in three planes and is described as pronation (a combination of eversion, abduction and dorsiflexion) and supination (a combination of inversion, adduction and plantar flexion) [1, 2]. The ankle joint is the major point for controlling sagittal plane movements of the leg relative to the foot, which is essential for bipedal ambulation over flat or uneven terrain [3]. The mid-tarsal joint represents the functional articulation between the hindfoot and midfoot. The interrelationship of the subtalar and mid-tarsal joint provides full pronation and supination motions throughout the foot. The first metatarsophalangeal joint (MTPJ) incorporates the first metatarsal head (MTH), the base of the proximal phalanx and the superior surfaces of the medial and lateral sesamoid bones within a single joint capsule. The main motion of the first MTPJ and the lesser MTPJs is in the sagittal plane (dorsiflexion and plantar flexion). During propulsion, the body weight is moving forward over the hallux creating relative dorsiflexion of the first MTPJ. This occurs with the hallux planted firmly on the ground and with the heel lifting for propulsion. The force acting across the first MTPJ approximates body weight, while the force across other MTPJs is considerably less [4]. Maximum loading of the first MTH and hallux is practically at the same time during stance in normal gait, highlighting the importance of the load-bearing function of both the hallux and first MTH.

During gait, the foot is required to be unstable at first for shock absorption and to adapt to the terrain, while during the propulsive phase the foot has to be stable to function as a lever. Foot flexibility and rigidity are mainly controlled with pronation and supination of the subtalar and mid-tarsal joints. As subtalar joint pronation after heel strike is a major shock-absorbing mechanism, limited joint mobility (LJM) or structural abnormality could compromise flexibility and shock absorption, thereby placing increased stress on the plantar skin surface [5, 6]. In addition, limited ankle dorsiflexion could result in increased pressure on the forefoot, particularly during the late stance phase of gait, caused by an early heel rise or compensatory pronation [5, 7, 8].

Gait Cycle

The gait cycle consists of two parts: the stance and the swing phase. The stance or weight-bearing phase can be divided into three parts; the first one is the contact phase initiated by initial contact to toe-off of the opposite limb. Normally, the first area of the foot in contact with the ground is the heel; however, in some cases, initial foot contact is with a flat foot. In cases of a midfoot deformity such as a Charcot joint, the midfoot could be the site of initial contact or the forefoot in case of a foot drop (anterior tibialis muscle weakness) or an ankle equinus (ankle plantar flexion contracture). The mid-stance phase begins with opposite-side toe-off and full forefoot loading and terminates with heel-lift. The third phase, the propulsion phase, can be further subdivided into two phases: active propulsion and passive lift-off. Active propulsion begins with heel-lift of the support-side and ends with

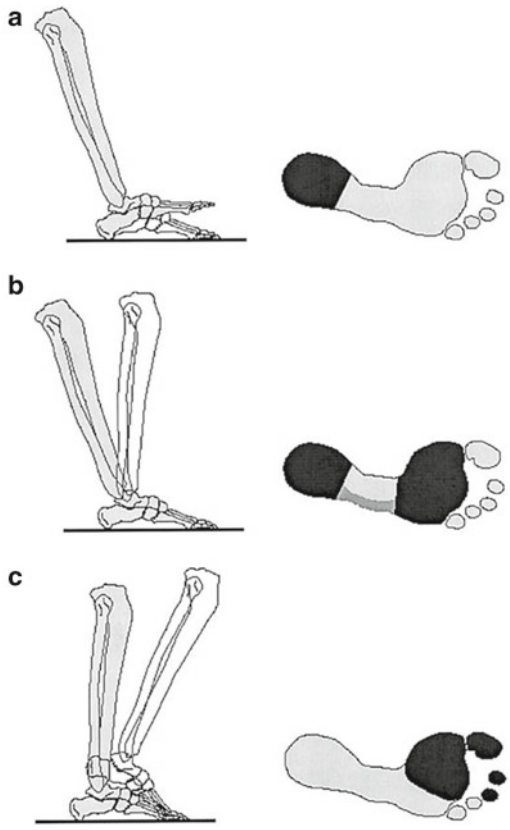

Fig. 11.1 Rocker action of the foot and ankle. The foot first rotates around the heel (heel rocker; **a**), then the ankle (ankle rocker; **b**), and then the metatarsal heads and toes (forefoot rocker; **c**). The plantar contact surface is shown at right (*dark*) (adapted with permission from Van Deursen R. Mechanical Loading and off-loading of the plantar surface of the diabetic foot. Clin Infect Dis (2004) 39 (Supplement 2): S87–S91)

opposite-side heel strike. During this stage, the greatest horizontal and vertical forces are directed against the foot and weight bearing is over a relatively small area (forefoot). It is, therefore, not surprising to find that the highest pressures are usually observed during this part of the stance phase. The passive lift-off begins with opposite heel contact and terminates with support-side toe-off.

Foot Rockers

Each part of the stance phase is characterised by a rocker action of the foot and ankle (Fig. 11.1). During the contact phase, the heel ("heel rocker") serves as an axis to allow smooth plantar flexion and to make full contact with the ground. During mid-stance, the ankle ("ankle rocker") allows the tibia to advance forward over the foot, causing relative dorsiflexion of the ankle. This advances the centre of pressure from the heel and midfoot to the forefoot. During active propulsion and passive lift-off, the first MTPJ ("the forefoot rocker") allows progression of the limb over the forefoot and accelerates heel-lift. Thus, normal joint mobility in the foot and ankle is necessary to allow for normal foot function as described.

Changes in the Foot Caused by Diabetes

Diabetic foot ulceration occurs as a consequence of the interaction of several contributory factors. Peripheral neuropathy is believed to cause changes in foot function and structure (i.e. MTHs), as well as dryness of the skin, which can lead to excessive callus formation [9–11]. Another important predictive risk factor for the development of diabetic foot ulceration is high plantar foot pressure [12, 13]. High foot pressures usually occur at sites with bony prominence, and have been strongly associated with reduced plantar tissue thickness [14, 15]. In addition, foot deformities are strongly associated with and predictive of increased plantar pressures and foot ulceration [11, 16, 17]. Prominent MTHs have traditionally been attributed to weakness of the intrinsic muscles of the foot leading to toe deformities. Fat cushions under MTHs, which are imbedded in the flexor tendons, are believed to migrate distally with clawing and hammering of the toes, leaving the MTHs relatively unprotected [18, 19]. Evidence for atrophy of these muscles has been demonstrated as fatty infiltration in plantar muscles of diabetic patients with a history of foot ulceration [20]. However, more recent evidence has shown foot muscle atrophy in patients with diabetic neuropathy while there was no relationship between toe deformities and muscle atrophy, suggesting that intrinsic muscle atrophy is either not the primary causative factor or that loss of foot muscles precedes the development of toe deformities [21, 22]. In a subsequent study, it was shown that diabetic neuropathic

patients with a toe deformity have greater reduced sub-MTH padding compared to patients without this deformity, indicating increased probability of high pressure and risk for foot ulcer development at these sites [23].

Plantar Tissue

The assessment of plantar tissue thickness in the forefoot has been suggested as an alternative method to pressure measurements. Plantar tissue thickness is strongly associated with plantar pressure, indicating a close relation between the amount of cushioning (soft tissue) available and the pressure distribution over the forefoot [14, 15]. Similarly, a strong relationship has been demonstrated between tissue thickness and history of ulceration in diabetic patients [24, 25]. Qualitative changes of the plantar fat pad have also been observed in the form of a non-specific fibrotic process beneath the MTH in patients with diabetic neuropathy. This fibrotic tissue affects the intrinsic biomechanical properties of the plantar fat pad to act as a shock absorber and dissipate increased plantar pressures associated with neuropathy [26]. Changes in tissue, such as degradation and interruption of the subcutaneous fat plantar to the first MTPJ, have also been found in clinically asymptomatic neuropathic feet of people affected by leprosy [27] (Fig. 11.2). However, during a 5-year follow-up, no complications such as an ulcer developed; therefore, the clinical significance of these findings remains unclear [28].

Charcot Arthropathy

Charcot arthropathy usually causes gross deformation of the foot, thereby severely affecting functional use of the foot and causing abnormal pressure loading during walking. Peak plantar pressure in patients with Charcot arthropathy was shown to be higher compared to that in patients with a neuropathic ulcer [29]. Patients with partially amputated feet were also shown to show a shift in weight-bearing pattern [30, 31] and amputation of the hallux greatly increases pressure under the MTHs [32, 33].

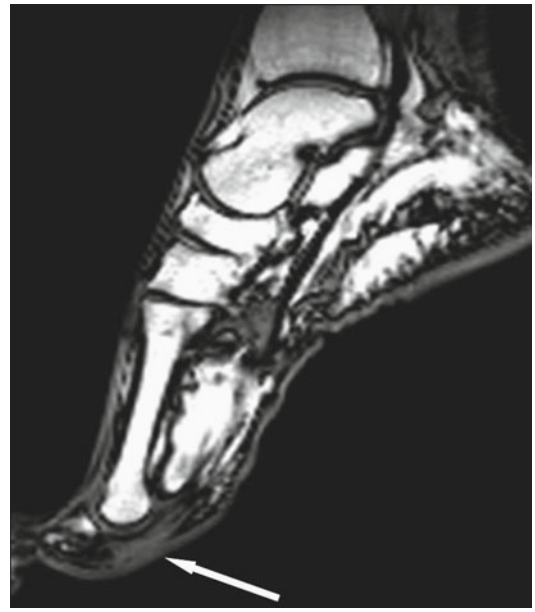

Fig. 11.2 MRI Illustrations of neuropathic feet of a person affected by leprosy. The MRI of the foot shows interruption of the subcutaneous fat plantar to the first metatarsophalangeal (MTP) joint (*white arrow*)

Callus

Callus has also been reported to be highly predictive for foot ulceration [34]. Callus acts as a foreign body, and its removal leads to reduction of plantar pressure in most cases [35, 36]. Furthermore, neuropathic ulcers are commonly found beneath plantar calluses, therefore frequent removal of callus is strongly recommended in diabetic patients.

Multivariate Predictive Models

Thus, several factors have shown to be related to increased foot pressure. Therefore, in an attempt to understand which factors are most important,

investigators have used multivariate modelling to study the independent contribution of factors. MTPJ angle (hammer toe deformity, a structural factor) was shown to be the most important variable predicting plantar pressure in forefoot regions in persons with diabetes [37]. Similarly, structural factors (radiographic measurements) were shown to be dominant in predicting peak pressure at the first MTH, although both structural and functional factors were among the most important contributors to peak pressure at the heel and hallux [38]. This indicates that contributing factors are region specific [38]. In contrast, in another study, neuropathy-related variables were shown to be more important than structural radiographic angles, soft tissue thickness and muscle strength in predicting peak pressure [39]. In a recent study, it was shown that for most foot regions a combination of clinical and radiological measurements was slightly better at predicting high pressure than clinical or radiological measurements alone [40]. However, since there was a considerable underestimation of high plantar pressure for either of the prediction models, this suggests that the use of quantitative pressure measurement tools should be used when accurate pressure readings are required. It should also be kept in mind that because there are many different factors that contribute to increased foot pressure the result of multivariate modelling will depend on which of those factors are selected to be studied as well as the selection of region of interest. Therefore, differences between studies in contributing factors will also be related to the research questions posed.

Not only foot deformities, but also functional and structural factors such as quantity and quality of the plantar cushioning, are indicators of abnormal foot loading during walking, thereby causing high plantar foot pressures. Alleviation of high pressure is best achieved with accommodative footwear, including insoles and shoes. It is important to ensure that the altered foot shape is properly fitted and accommodated in the footwear. For many patients, normal high street footwear will not meet these criteria.

Limited Joint Mobility (LJM)

Joint mobility is defined as the range of motion of a joint and is related to age, sex and ethnic background [41–43]. LJM of the foot and ankle has been suggested to increase plantar pressure in diabetic patients [44, 45] and to be related to foot ulceration [46, 47]. The aetiology of LJM is unknown, although most evidence favours a relationship with the collagen abnormalities and non-enzymatic glycation of soft tissue that occurs in diabetes, resulting in thickening of skin, tendons, ligaments and joint capsules, thereby reducing tissue flexibility [48, 49]. The prevalence of LJM (diagnosed with a positive "prayer sign") has been reported to vary between 49 and 58% for Type 1 diabetic patients and between 45 and 52% for Type 2 patients [50–52].

Joint mobility of the subtalar joint was shown to be significantly reduced in the ulcerated foot compared to the contralateral non-ulcerated foot in diabetic neuropathic patients [46]. The same authors also reported an association between mobility of joints of the hand and foot, indicating that stiffening of joints appears to be a general feature in diabetic patients. Similarly, ankle dorsiflexion and subtalar range of motion were reduced in diabetic patients with a history of plantar ulceration compared to patients without ulceration and non-diabetic controls [47]. In addition, ulceration of the great toe has been associated to a reduced range of motion at the first MTPJ [8]. Figure 11.3 illustrates the relationship between reduced first ray range of motion (first MTH dorsiflexion) and increased pressure at the first MTH in patients with a history of first MTH ulceration as opposed to no apparent relationship for patients with a history of plantar forefoot ulceration not at the first MTH [8].

The suggested explanation for the link between LJM and foot ulceration comes from studies showing a relation between joint mobility at the subtalar and ankle joint and foot pressures [53]. Similarly, Andersen and Mogensen [54] reported that maximum movements at the ankle were delayed and

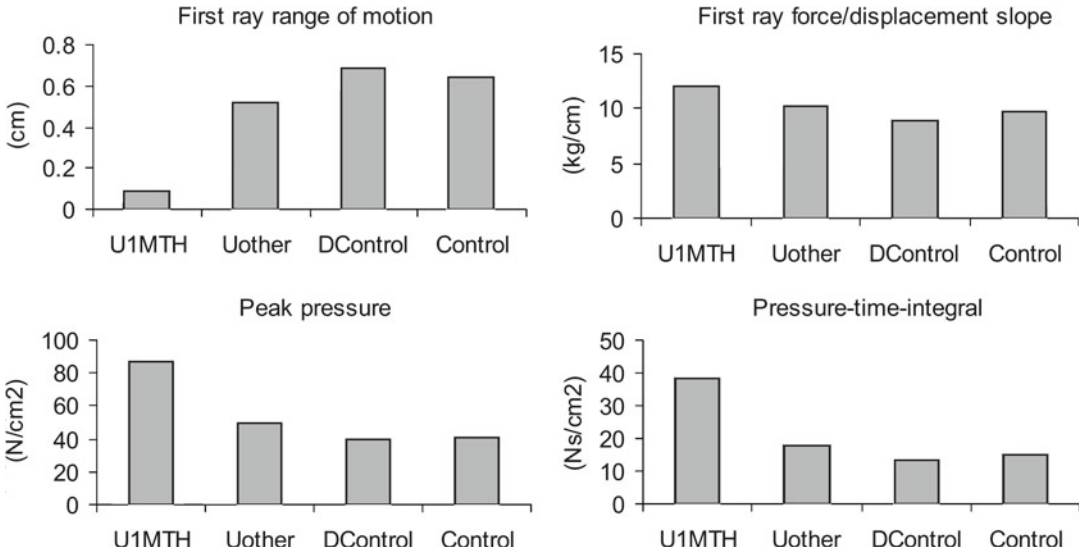

Fig. 11.3 Range of motion and plantar pressure of first metatarsal head (MTH). First ray dorsiflexion was measured as vertical displacement of the first MTH, while the second through the fifth MTHs were stabilised. The force (up to 8 kg) applied to and the vertical displacement of the first MTH was measured simultaneously. Pressure under the first MTH was measured during barefoot walking at standardised walking velocity. U1MTH = patients with a history of ulceration at first MTH, Uother = patients with a history of plantar forefoot ulceration not at the first MTH, DControl = diabetic patients without a history of foot ulceration and Control = non-diabetic controls. The U1MTH group had a significant stiffer first MTH and higher pressure under the first MTH as compared to the other three groups ($p < 0.05$) (based on Birke et al., (1995), ref. [8])

slowed using an isokinetic dynamometer in long-term Type 1 diabetic patients. In contrast to the above studies, another study could not report a clear relationship between joint mobility of the foot (i.e. subtalar, ankle and first MTPJ) and plantar pressures. The only joint mobility measurement related to plantar pressure was the measurement in the hand (extension of the fifth metacarpophalangeal joint) [55], suggesting that this may be a surrogate marker for diabetic complications in general which could therefore explain the association with increased foot pressures. More recent evidence was shown in favour of no direct relation between LJM and increased pressure. Turner and colleagues showed that even in case of significant reduction in passive ankle ROM in diabetic patients gait ROM (dynamic ROM) was not different from control subjects and not correlated with plantar pressure (Fig. 11.4). However, at the first MTPJ, passive and gait ROM were correlated with plantar pressure and it was concluded to be the preferable joint for ROM measurement [56]. Other evidence showed that although there is a relation between ankle equinus (ankle plantar flexion contracture), it only accounts for a small proportion of variance of pressure, suggesting a limited role for ankle equinus in increasing forefoot pressure [57].

Thus, although joint mobility appears to be reduced in diabetic patients, it is important to note that the relationship with foot ulceration has only been studied retrospectively. The interpretation of this could be that foot ulceration causes stiffening of the joints as opposed to LJM causing foot ulceration. Foot ulcers are frequently healed using casts for offloading and in addition patients are advised to minimise their level of physical activity while healing the ulcer; these two factors are quite likely to compromise joint mobility. Furthermore, it is also important to realize that although joint mobility may be reduced it may still be within the range of motion required for normal walking.

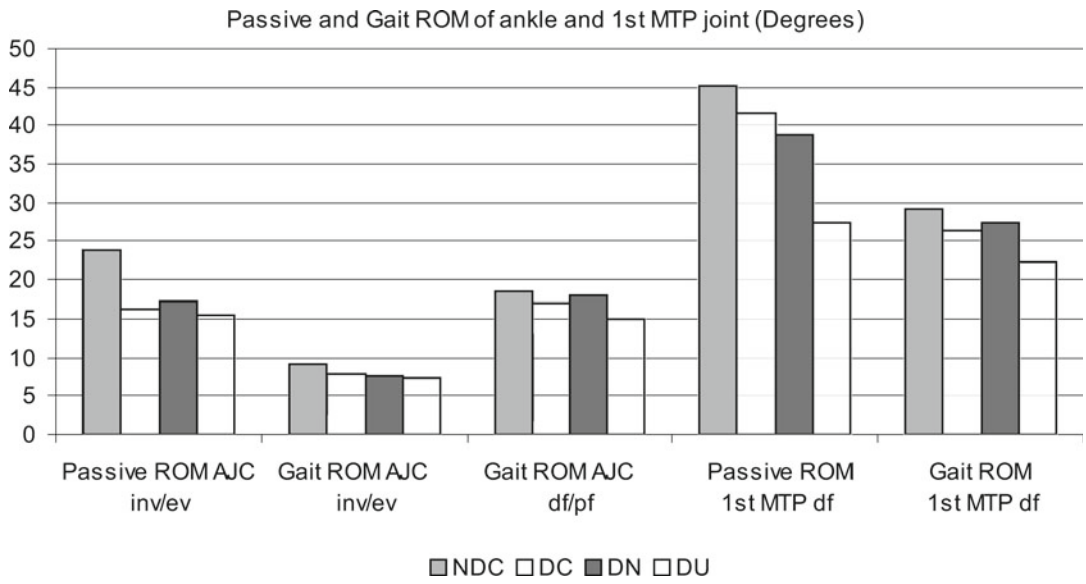

Fig. 11.4 Passive and gait range of motion at the ankle joint complex and first metatarsophalangeal joint for the non-diabetic controls (NDCs), diabetic controls (DCs), diabetic neuropathic group (DN) and diabetic (current or past) ulceration group (DU). Joint motion analysis was undertaken using a 3D electromagnetic tracking system. The variables measured during gait were maximal inversion/eversion and dorsiflexion/plantarflexion ROM at the AJC and maximal dorsiflexion at the first MTP joint. The variables measured passively were maximal inversion/eversion ROM at the AJC and maximal dorsiflexion at the first MTP. The passive ROM was determined by standard non-weight-bearing clinical ROM tests with the electromagnetic tracking sensors attached. *Passive ROM* passive range of motion, *gait ROM* gait range of motion, *AJC* ankle joint complex, *INV/EVE* inversion/eversion motion, *DF/PF* dorsiflexion/plantarflexion, *MTP* metatarsophalangeal joint, *DF* dorsiflexion (based on Turner et al., (2007), ref. [57])

Balance and Gait Abnormalities in Diabetes

Patients with diabetic distal peripheral neuropathy may experience instability while walking or standing, which is attributed to the general loss of peripheral sensory receptor function in the lower legs. Diabetic neuropathy is associated with an increased risk of falls and an increased risk of developing fractures [58, 59]. Fall prevention is, therefore, warranted in people with diabetes. Although in itself this does not immediately pose a risk for foot ulceration, the fact that fractures are often healed using casts suggests that altered gait and balance during the healing period may increase the risk of altered limb loading of the affected and unaffected limb.

Walking and Mobility

Besides the effect of peripheral neuropathy on reduced postural stability, there is also increasing evidence of the effect of diabetes and neuropathy on mobility during daily life activities [60]. Studies have shown that diabetes is associated with an increased risk of being unable to do mobility-related tasks and physical limitation [61–63].

With regard to the effect of foot complications on walking, walking capacity and daily walking activity have been investigated in diabetic patients with neuropathy, active plantar foot ulcer, partial foot amputation and trans-tibial amputation [64]. The results showed a reduced gait velocity, average daily stride count and increased total heartbeat index (energy expenditure) towards the group

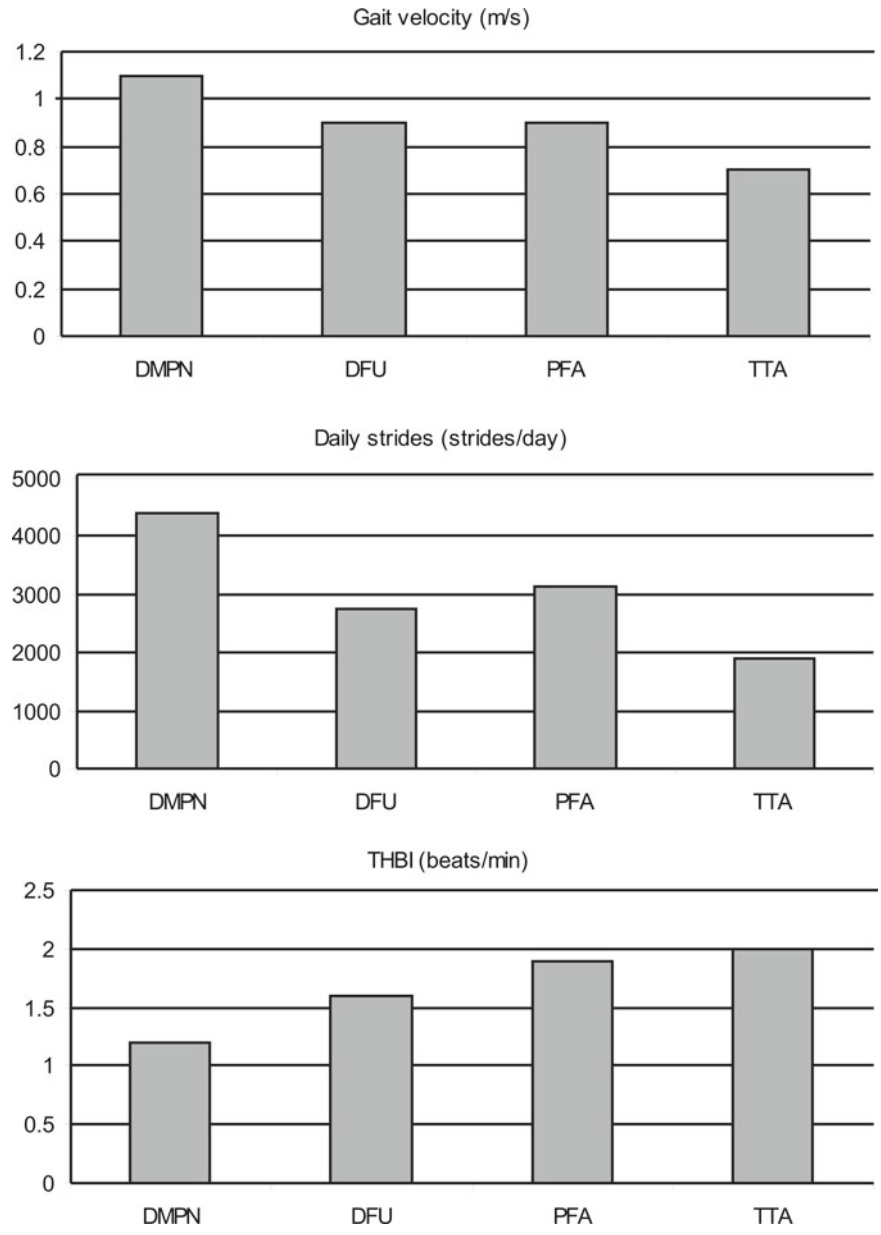

Fig. 11.5 Functional capacity and performance of walking decline with progression foot complications. The capacity for walking was measured using the total heartbeat index (THBI), which was calculated as an index of energy expenditure during a 2-min walking test. THBI was calculated as the ratio of the total number of heartbeats to the total distance covered. Gait velocity and average daily strides were measured to assess the performance of walking. Gait velocity was the average self-selected walking speed over three trials of 12 m. Step activity monitors (SAMs) were used to record the performance of daily walking activity. The average number of strides from 8 consecutive days was taken. Diabetic patient groups: *DMPN* diabetic neuropathy, *DFU* current plantar foot ulcer, *PFA* partial foot amputation, *TTA* trans tibial amputation (based on Kanade et al., (2006), ref. [64])

with more severe complications. Figure 11.5 demonstrates this decline in the functional capacity and performance of walking with the progression of diabetic foot complications [64]. Similarly, more gait disturbances were shown when amputation levels become more proximal. Transmetatarsal, Lisfranc and Chopart amputation can all result in loss of power generated across

the ankle with significant wasting of the triceps surae muscles and limitations in stability and subsequently adaptive gait [65]. In another study by Kanade and colleagues, it was reported that adaptations in gait and daily walking activity in patients with unilateral trans-tibial amputation affect the plantar pressure distribution and ultimately the potential risk of ulceration to the surviving foot. Prolonged plantar load bearing (higher pressure time integral (PTI) and slower average velocity of centre of pressure) with decreased plantar cumulative stress exacerbates the potential risk of plantar injury in the surviving foot [66].

Gait Pattern and Muscle Activation

Peripheral neuropathy not only affects postural stability but also gait. Gait of diabetic neuropathic patients was shown to be more conservative and characterised by decreased speed and stride length, as well as a greater time spent in double-support phase compared to age-matched control subjects [67]. Additionally, reaction times during walking were longer in the diabetic patients compared to control subjects, suggesting that peripheral neuropathy required the patients to allocate a greater proportion of their attention to the walking task [67]. It could be that the more conservative gait pattern in the diabetic neuropathic patients may help to reduce attentional demands that are necessary to control gait. The findings from this study indicate the importance of proprioception in the control of human gait.

Others have reported a reduced ankle joint moment and power during gait in neuropathic patients compared to non-diabetic controls, resulting in reduced walking velocity and step length [53]. In another study, diabetic patients with neuropathy were shown to have more co-contraction of agonist and antagonist muscles at the ankle and knee joints during stance phase compared with control subjects while they walked slower and had reduced joint moments at the ankle and knee [68]. These changes may allow diabetic neuropathic patients to walk with a safer and more stable gait pattern. The activation of the soleus and medial gastrocnemius muscles in diabetic neuropathic patients was premature and, therefore, could be contributing to abnormal forefoot plantar pressure distribution [68]. Both previous studies investigated patients with a history of ulceration, which may have been a covariate as previous ulceration and consequent wearing offloading devices may also have affected their gait pattern. Abboud and colleagues [69] showed a delayed firing of the anterior tibialis muscle after initial foot contact. This means that the normal modulating role of the anterior tibialis muscle in lowering the foot to the ground through eccentric contraction is disturbed and causes less control over lowering the (fore) foot which may cause high plantar pressure [69].

On a similar note, a recent study showed that independent of walking speed people with diabetes or diabetic polyneuropathy adjust the timing of muscle activity. The delayed cessation of muscle activity suggests that there is a reduced rate of force development, which underlies the adjusted timing of muscle activation. [70]. In an earlier publication by the same authors, it was suggested that reduced capacity to control the forward displacement of the centre of pressure results in a redistribution of plantar pressures under the foot [71].

Thus, various studies have shown that diabetic peripheral neuropathy is related to postural instability, gait abnormalities and reduced walking activity and mobility. It has been suggested that altered gait may have consequences on daily plantar pressure loading and hence risk of foot ulceration.

Development of Diabetic Foot Ulceration

Foot ulcers in diabetes result from multiple pathophysiological mechanisms, including roles for neuropathy, peripheral vascular disease, foot deformity, higher foot pressures and diabetes severity [72]. Diabetic neuropathy and peripheral vascular disease are the main aetiological factors which predispose to foot ulceration and may act alone, together, or in combination with other factors, such as microvascular disease, biomechanical abnormalities and an increased susceptibility to infection [72–75]. Trauma is needed in addition to neuropathy and vascular disease to cause tissue breakdown. Trauma could be intrinsic, such as

repetitive stress from high pressure and/or callus, or extrinsic, such as from ill-fitting footwear rubbing on the skin or an object inside the shoe (e.g. drawing pin, pebble).

As trauma, and therefore the risk of foot ulceration, can be minimised, it is important to identify insensitive feet at risk of ulceration in order to implement preventative care, such as the provision of appropriate foot care, education and referral for podiatry treatment.

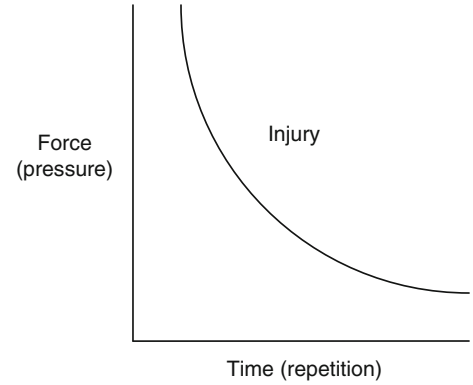

Fig. 11.6 Inverse relationship between force (pressure) and time (or repetition). As force (pressure) increases, the duration (time) or number (repetition) of force(s) required to cause tissue injury decreases (based on Kosiak et al., (1959), ref. [77])

Biomechanical Aspects of Foot Ulceration

Ulcer sites are predominantly under the plantar surface of the toes, forefoot and midfoot, followed by the dorsal surface of the toes and heel [11]. As high plantar foot pressures are an important factor in the pathogenesis of diabetic foot ulceration, the proposed mechanism of pressure-induced ulcers is discussed next.

Skin is the mechanical link through which intrinsic forces are transmitted to the outside world and environmental forces to the skin and subcutaneous tissue. Ulceration seems to be caused by repetitive and/or excessive pressure on the surface of the insensitive skin leading to tissue damage. If the same pressures occurred in a person with adequate sensation, the person would experience pain and avoid the offending pressures. However, in a person with loss of protective sensation, there is no warning of excessive pressures or tissue damage and persistent localised pressures could lead to skin breakdown or ulceration. Foot deformities are usually responsible for these excessive pressures. In addition, healing of plantar ulcers is prevented as long as patients keep walking on their foot wounds, thus highlighting the key issue of mechanical offloading.

Thus, excessive and/or repetitive pressures appear to be the main causative factor for development of skin breakdown. There are three mechanisms that account for the occurrence of these pressures: (1) increased duration of pressures, (2) increased magnitude of pressures or (3) increased number of pressures [76]. The first mechanism includes relatively low pressures applied for a long period of time causing ischaemia. Prolonged ischaemia leads to cell death and wound formation, as has been demonstrated in a classic experiment [77]. An inverse relationship was shown between time and pressure and is shown in Fig. 11.6. High pressures took a relatively short time to cause ulceration while low pressures took a relatively long time. Thus, ulceration can develop at very low pressures, but may take a few days to occur. This type of offending pressure and resulting ulcers can occur with ill-fitting footwear, improperly fitted orthotics or prolonged resting of a heel on a bed or footrest.

The second mechanism of tissue injury includes high pressures acting for a short time period. This injury only happens if a large force is applied to a relatively small area of skin. This happens, for example, if a person steps on a nail or piece of glass, which is not unusual for diabetic neuropathic patients. Alternatively, a “foot slap” may also conform to this mechanism. A “foot slap” indicates a reduced deceleration of the forefoot after heel strike caused by weak dorsiflexion muscles. It has previously been demonstrated that high rates of tissue deformation lead to cellular death while comparable gradually applied

loads do not [78]. It is, therefore, suggested that control of the velocity of the forefoot descending after heel strike by using ankle-foot orthosis could possibly help in prevention of diabetic foot ulcers.

The third mechanism of injury comes from repetitions of pressure, which in engineering terms would lead to an equivalent syndrome of mechanical fatigue. Mechanical fatigue is defined as failure of a structure or biological tissue at a sub-maximal level to maintain integrity due to repeated bouts of loading. This type of injury seems to occur in the insensitive skin and subcutaneous tissue of the neuropathic foot.

The body will respond to repeated high pressures or micro-trauma with callus formation in order to protect the skin from further damage. However, if callus formation becomes excessive, it will contribute to higher pressure, and should therefore be removed at a regular interval [35, 36].

Activity Level

Although a high level of activity has traditionally been regarded as "repetitive stress" and therefore considered as a risk factor for diabetic foot ulceration, interesting new evidence has shown that patients who were less active were more likely to develop foot ulceration [79, 80]. In addition, the risk may not be related to the level of activity but the increased variability in physical activity, which was recently shown to be associated with the development of foot ulceration [81]. Furthermore, the just described lower daily activity in patients with previous ulceration resulted in lower daily cumulative stress (pressure time integral × daily strides). The finding that cumulative stress in patients with previous ulceration was lower than in control and diabetic patients without previous ulceration is consistent with the theory that plantar tissue in patient with previous ulceration may be susceptible to tissue breakdown at relatively low levels of cumulative stress [79]. Similarly, a study in persons affected by leprosy showed that cumulative stress was not different between persons without previous ulceration, with previous ulceration or with current ulceration, suggesting again that tissue in persons with ulceration may be more vulnerable to stress [82].

Thus, not only the magnitude of the plantar pressure is important in causing foot ulceration, but also several other factors such as the rate of increase of pressure, duration of high pressure and the frequency of applied pressure to the skin should be taken into account. In addition, although foot pressures may be high during a barefoot pressure assessment, it is important to keep in mind that it is the combination of footwear, lifestyle factors, tissue characteristics, foot pressures and level of physical activity which contribute to the development of foot ulceration. In addition, the effect of physical activity and daily cumulative stress on the development of foot ulceration is an area that deserves further exploration.

Foot Type and Foot Ulceration

Feet with "abnormal" alignment of the forefoot or rearfoot exhibit a different loading pattern than normally aligned feet. Both non-diabetic and the diabetic planus feet (everted rearfoot, inverted forefoot and low arch) have shown to experience greater peak pressures than non-diabetic rectus feet (a neutral rearfoot and forefoot with normal arch morphology) [83]. This is in agreement with previous reports of an association between type of foot deformity and callus and ulcer location in a group of diabetic patients with active ulceration [84]. In this particular study, 88% (15/17) of patients with an uncompensated forefoot varus or forefoot valgus (in- or everted forefoot) had ulcers located at the first or fifth MTH. Similarly, an inverted heel position has been associated with lateral ulcers, whereas an everted heel position was associated with medial ulcers [85].

Thus, high pressures may not just be caused by the effects of diabetes; therefore, it seems reasonable to hypothesise that diabetic patients with foot-type characteristics that differ from the norm are more likely to develop high foot pressures and ulceration than diabetic patients with normal foot morphology.

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Diabetic Foot Ulcers: Effects of Hyperoxia and Stromal-Derived Factor-1α on Endothelial Progenitor Cells

12

Ying Zhuge, Sharyce Gonzalez, and Omaida C. Velazquez

Abstract

In order for cutaneous wounds to heal in a timely manner, many requisites must be fulfilled, including infection control, resolution of inflammation, proper cell migration, differentiation, proliferation, deposition of extracellular matrix (ECM), sufficient delivery of oxygen and nutrients, wound contraction, and reepithelialization (Lazarus et al. Arch Dermatol 130: 489–93, 1994). These events in turn require proper immune status, active angiogenesis/vasculogenesis, and avoidance of negative mechanical forces, such as weight bearing (Liu and Velazquez Antioxid Redox Signal 10:1869–82, 2008). Of all the above conditions, the most critical component for normal healing of full-thickness wounds is the formation of new blood vessels within the granulation tissue.

Keywords

Diabetic foot ulcers • Endothelial progenitor cells • Hyperoxia • HBO • Stromal-derived growth factor-1α

Introduction

In order for cutaneous wounds to heal in a timely manner, many requisites must be fulfilled, including infection control, resolution of inflammation, proper cell migration, differentiation, proliferation, deposition of extracellular matrix (ECM), sufficient delivery of oxygen and nutrients, wound contraction, and reepithelialization [1]. These events in turn require proper immune status, active angiogenesis/vasculogenesis, and avoidance of negative mechanical forces, such as weight bearing [2]. Of all the above conditions, the most critical component for normal healing of full-thickness wounds is the formation of new blood vessels within the granulation tissue [3]. Neovascularization in the granulation tissue occurs from angiogenesis, whereby resident endothelial cells of preexisting vessels in the wound proliferate and remodel

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into new vessels, as well as vasculogenesis, during which the endothelial progenitor cells (EPCs) from the bone marrow (BM) are recruited and undergo in situ differentiation and maturation to give rise to new vessels [4, 5]. When any component of this complex wound healing process is compromised, chronic wounds occur, which either requires more than 8 weeks to heal, or not heal, or recur [1, 2].

The most prevalent forms of chronic wounds are leg ulcers caused by vascular insufficiency and foot ulcers associated with diabetes [6, 7]. Wound healing in diabetes mellitus is altered due to both macrovascular and microvascular processes, and while the former can be addressed with surgical intervention, the latter is more difficult to correct. Neovascularization within the granulation tissue via angiogenesis and vasculogenesis is critical for wound healing, and EPCs have been implicated in these processes. Mobilization of these important progenitor cells from the bone marrow is impaired in diabetes, which combined with the abnormal homing of EPCs that also occurs in diabetes, leads to stunted wound healing in diabetic foot disease.

Current therapies for diabetic wounds focus on prevention, early diagnosis, and treatment methods, such as sharp debridement, antibiotic therapy, revascularization when necessary, and offloading [8]. However, these therapies do not address the underlying microangiopathy that is inherent in diabetic foot ulcers. Recently, focus has been placed on these BM-derived EPCS and their roles in the small vessel disease that is prevalent in diabetic patients, and discoveries have been made regarding the interaction of the BM as well as the peripheral wound in the mobilization and homing of these cells. Recent studies show that hyperoxia and administration of exogenous stromal-derived factor-1α increase circulatory and wound levels of EPCs and improve wound healing in diabetic mice. These findings have great potential in translating into human counterparts as the treatment for this prevalent disease matures [8–12].

Effect of Diabetes on BM-Derived EPCs

EPCs are embedded in a microenvironment (niche) of the BM and can mobilize into circulation in response to trauma or ischemia [13], home to specific sites where neovascularization is needed by chemokines and growth factors, undergo in situ differentiation, and participate in the formation of new vessels [14] (Fig. 12.1). While the precise mechanism of EPC mobilization from BM is not clearly delineated, one proposed pathway involves the activation of endothelial nitric oxide synthase (eNOS) in the BM by vascular endothelial growth factor

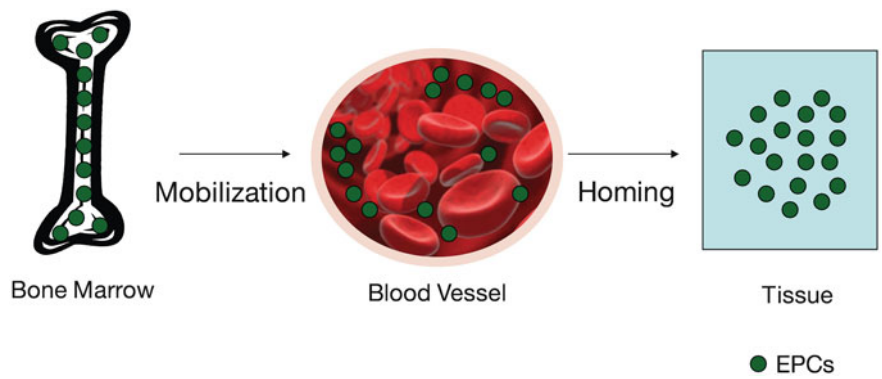

Fig. 12.1 Endothelial progenitor cells mobilize from the bone marrow into circulation, home to specific sites where neovascularization is needed by chemokines and growth factors, undergo in situ differentiation, and participate in the formation of new vessels

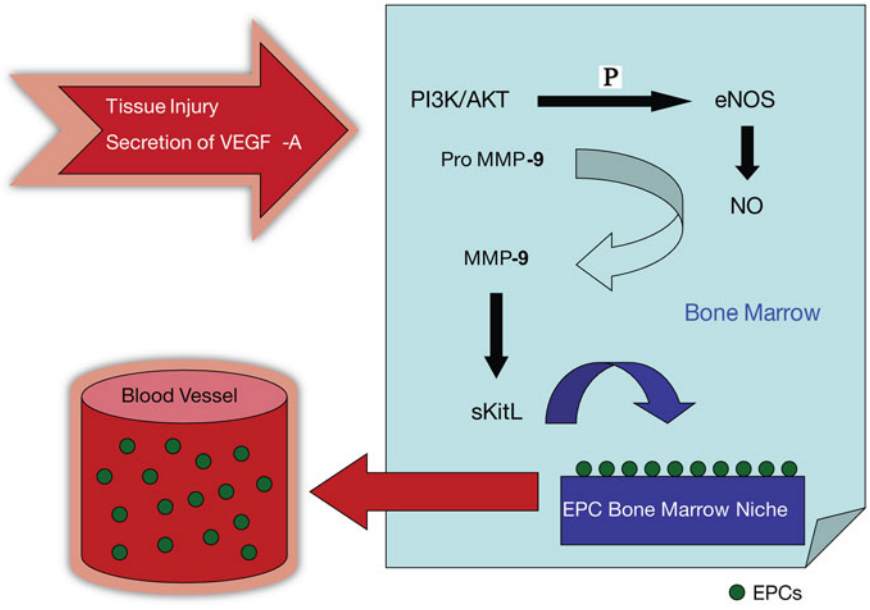

Fig. 12.2 Increases in nitric oxide levels in the BM are critical to mobilization of EPCs from the BM niche. After its own activation, eNOS causes induction of matrix metalloproteinase 9 (MMP-9) in the BM, and activated MMP-9 then brings about the release of the soluble Kit ligand, which shifts endothelial progenitor and hematopoietic stem cells into a proliferative state in the niche, inducing their subsequent mobilization into the circulation

(VEGF)-A, which is increased in ischemia and peripheral wounding [15, 16]. eNOS catalyzes the stepwise oxidation of L-arginine to produce citrulline and nitric oxide (NO) [17, 18], which has been demonstrated that it plans an essential role in endothelial cell proliferation, and is a central mediator of several endothelial growth factors, one of which is VEGF-A2. Increases in NO levels in the BM are critical to the mobilization of EPCs from their niches [19, 20]. After its own activation, eNOS cases induction of matrix metalloproteinase (MMP)-9 in the BM, and activated MMP-9 then brings about the release of the soluble Kit ligand, which shifts endothelial progenitor and hematopoietic stem cells into a proliferative state in the niche and brings about subsequent mobilization [21, 22] (Fig. 12.2).

EPCs have been shown to contribute to various forms of neovascularization, such as during wound healing [23], limb ischemia[5, 24], postmyocardial infarction [25], endothelialization of vascular grafts [2], atherosclerosis [26], neonatal vascularization [27], and tumor growth [28, 29]. In many of these reported studies, increased levels of EPCs were identified in the tissues and recruited EPCs contribute significantly to neovascularization. In contrast, reduced levels and impaired function of EPCs have been described in both type 1 and 2 diabetes [30, 31] which is likely to be involved in the pathogenesis of wound-healing complications in diabetes.

Many studies have shown that the ischemia-induced increase in circulating EPCs does not occur in diabetes[3, 30–32]. Interestingly, this is not attributable to decreased numbers of progenitor cells in the BM niche, but rather to dysfunction in the release of these cells [8]. The decreased number of circulating EPCs in diabetes has two probably causes. One mechanism is impaired mobilization from the bone marrow, it has been shown, for example, that eNOS function is impaired in diabetes, which prevents EPCs from being released by their niche in BM and thereby decreasing number of circulating EPCs (*see* below) [14]. In addition, correction of the defect in eNOS-NO cascade has been demonstrated to recover downregulated EPC mobilization [14]. In addition, following hind limb ischemia, Xu et al. found

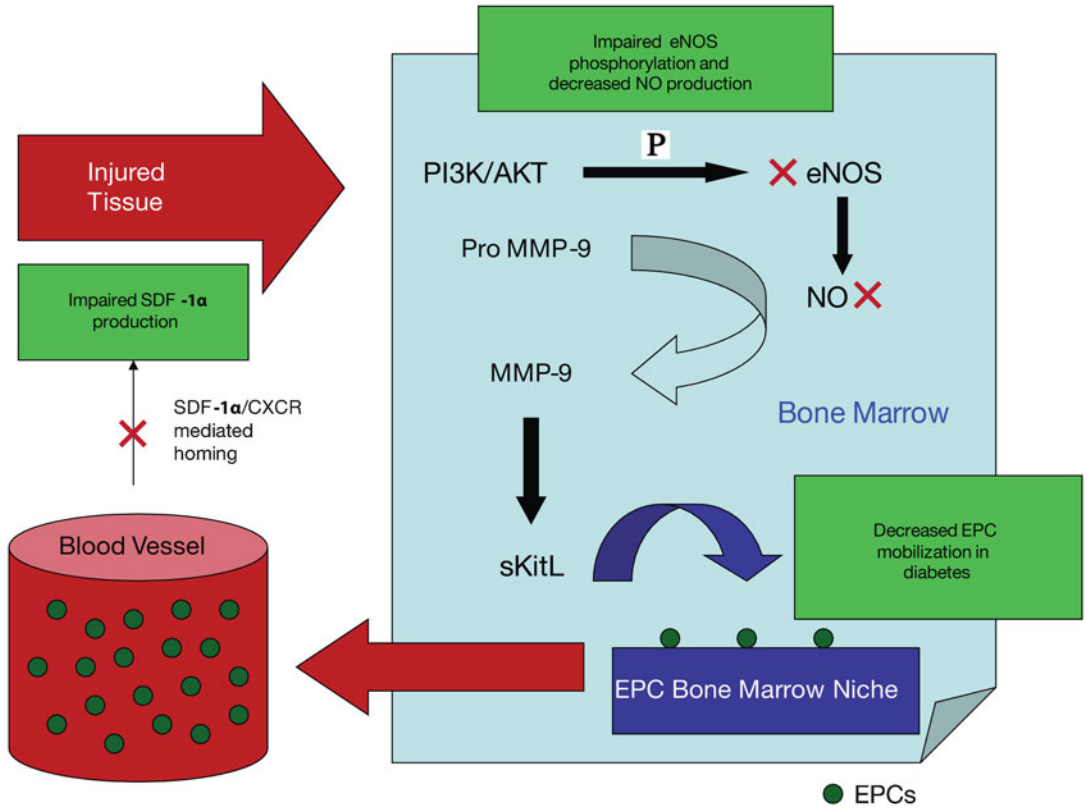

Fig. 12.3 In diabetes, SDF-1α production in the peripheral wound is impaired due to a decreased number of cells responsible for its production, i.e., epithelial cells and myofibroblasts. In addition, the hyperoxia-induced increase of NO in BM is attenuated, likely as a result of impaired eNOS phosphorylation. Therefore, there are both decreased circulatory numbers of EPCs (from impaired eNOS-mediated release) and diminished wound levels of EPCs (from decreased homing due to lack of SDF-1α from the wound)

that diabetic mice exhibited suppressed EPC mobilization, which leads to decreased postischemia neovascularization [33]. Another possible contributing factor to the decreased number of circulating EPCs in diabetic patients may be the consumptive loss of EPCs due to increased endothelial damage in these patients. Xu et al. showed that aortas from diabetic mice had increased endothelial damage when compared to nondiabetic controls. Also, diabetic mice had higher levels plasma endothelial microparticles (EMPs) in circulation, which is a reflection of chronic endothelial damage, and lower levels of circulating EPCs when compared to nondiabetic controls [33].

In addition, the homing of circulating EPCs is compromised in diabetes, as critical chemokines involved in attracting these cells to the site of neovascularization are significantly decreased in the diabetic wound (see below). For example, diabetic mice show impaired ischemia-induced up regulation of VEGF, hypoxia-induced factor (HIF)-1α, which decreases homing of these critical cells to areas where they are needed [33]. Therefore, impaired release and faulty homing of EPCs combine to bring about poor vascularization and the formation of chronic wounds in these patients (Fig. 12.3).

Hyperoxia and EPC Mobilization

Oxygen plays a key role in wound healing. Oxygen tension directly correlates with fibroblast replication [3, 34] collagen production [35], granulation tissue formation [36], bacterial killing [37], and enhanced bacteria-killing ability of leukocytes [36],

epithelialization [38], release of vascular growth factors by macrophages [39], and angiogenesis [40, 41]. Hyperoxia can also trigger the onset of signal transduction pathways that regulate the gene expression of growth factors and their receptors, such as PDGF [42]. Hyperoxic vasoconstriction also reduces capillary pressure and increases vascular permeability, leading to increased extravascular fluid resorption and reduced tissue edema [43]. While low oxygen tension around the wound enhances the progression of a chronic ulcer, hyperoxia aids in the healing process. Measurement of transcutaneous pressure of oxygen ($tcpO_2$) has been shown that patients with $tcpO_2$ values <20 mmHg have greatly increased rate of failure of wound healing when compared to patients whose $tcpO_2$ levels are >40 mmHg [40]. Hyperbaric oxygen (HBO) is a systemic treatment where patient breathes 100% oxygen for a specified period of time in a pressurized chamber [36, 40, 43]. It is the least invasive and most potent method of delivering high levels of oxygen tension to the wound. HBO is currently approved by the Food and Drug Administration (FDA) as a safe, adjunct therapy for chronic diabetic wounds. Patients receive ≥20 treatments with pure oxygen at 2.0–2.4 atm once to twice daily.

It has been shown that HBO increases BM NO levels via an eNOS-mediated pathway, which in turn triggers EPC mobilization into circulation in both nondiabetic mice and nondiabetic humans [4, 44]. Goldstein et al. and Thom et al. have shown that hyperoxia induced by HBO raises NO levels within femoral BM, augments EPC colony-forming capacity in vitro, and increases the number of BM EPCs in circulation and within cutaneous ischemic wounds in vivo. This leads to increased lower limb circulatory recovery after femoral ligation, as shown by laser Doppler flowmetry in ischemic wounds, and by day 8 after wounding, the ischemic wounds treated with HBO had significantly improved revascularization and faster wound closure [3, 4]. Mice exposed to sham pressurization showed no deviation in circulating cells compared to those exposed to 2.4 atm of oxygen [3]. Also, mice that were pretreated with NG-nitro-L-arginine methyl ester (L-NAME), a nonspecific NOS inhibitor, before treatment with HBO showed no change in the number of circulating EPCs and no improved wound healing, demonstrating that NOS is required for the release of EPCs from BM during activation [4].

Similar effects by HBO on eNOS activation and thereby EPC mobilizations from the BM have been shown in diabetic mice. For example, Gallagher et al. showed that BM isolated from streptozocin-induced diabetic mice had decreased levels of biologically active phosphorylated eNOS protein [14], and that the hyperoxia-induced increase of NO in the BM is attenuated in diabetes, likely as a result of this impaired phosphorylation of eNOS [14]. This diabetes-associated defect in the production of biologically active eNOS can be reversed by hyperoxia. In these studies, which used bone marrow cells chimeras to track the fate of bone marrow-derived cells, it was shown that increases in BM NO induced by hyperoxia stimulate mobilization of BM EPCs into peripheral circulation in diabetic mice. This was negated by L-NAME treatment, and this was also absent in eNOS −/− mice, indicating that eNOS is essential for hyperoxia-induced EPC mobilization [14]. Hyperoxia, via eNOS/NO-mediated mechanism, increases mobilization of EPCs from BM into circulation and reverses the preexisting circulating EPC deficit in diabetes, thus improving the numbers of EPCs potentially available for vasculogenesis and wound healing [14]. Therapeutic wound-healing effects of increased BM EPC mobilization into circulation and recruitment into wounds were observed in association with enhancement of neovascularization and faster healing of these wounds.

In the clinical setting, various studies have shown HBO to be an effective adjunctive therapy for chronic diabetic ulcers [45–48]. Faglia et al. conducted prospective, randomized trials that showed patients who received HBO to have a significantly lower rate of transtibial or more proximal amputations in comparison to standard therapy [46, 47].

Many other studies have also found similar decreases in the risk of major amputations in diabetic patients who receive HBO [36, 43, 49]. Duzgen et al. found in their prospective, randomized study of 100 patients, that in addition to being more likely to undergo amputation distal to the metatarsophalangeal joint (minor amputation),

patients in the HBO group were also more likely to heal their chronic wounds [43]. Kalani et al. performed a prospective study of 38 patients with chronic diabetic foot ulcers with long-term follow-up and found that 76% of patients who received HBO had healed with intact skin at 3 years, compared to only 48% of patients who did not receive HBO. They concluded that adjunctive HBO therapy can accelerate rate of healing, reduce the need for amputation, and increase the number of healed wounds on the long-term follow-up [36]. Kessler et al. found that after cessation of HBO therapy, the wound healing advantage disappears, which leads to the question of whether longer periods of HBO sessions would result in better healing [50]. In addition to systemic HBO, Gordillo et al. also studied the benefit of topical oxygen (TO) therapy on chronic wounds and concluded that TO significantly improves wound healing [51].

In addition to individual trials, other groups attempted to perform systematic analysis of HBO literature in order to provide generalized recommendations for this controversial and costly resource. Kranke et al. performed analysis of five trials on HBO and found that pooled data showed that adjunctive HBO reduced risks of major amputation as well as improve the chance of healing at 1 year the number needed to treat is four individuals to prevent one amputation in the short term [52]. They concluded that the use of HBO might be justified where facilities are available [52]. In 2009, a systematic review was performed that studied the efficacy of HBO for wound healing and limb salvage [4]. A total of 64 observational studies and randomized controlled trials on HBO and healing outcomes were included, and the study concluded that for patients with diabetic foot ulcers, HBO reduces rate of amputation and improves chance of healing [4]. However, Wunderlich et al. conducted a similar study and concluded that additional randomized placebo-controlled clinical trails in larger study populations are needed to lend credence to the presumption that HBO therapy can improve clinical outcomes in these patients [53]. Therefore, while many studies show improved wound healing in HBO therapy for diabetic patients and decreased amputation, large randomized, double-blinded trials are still necessary to bring about widespread acceptance of HBO as standard therapy for chronic diabetic wounds [53, 54]. The cause for such varied outcomes by these studies may be in part of their design. But also due to the fact that there may be responders as well as non-responders to HBO, and that it is important to identify specific conditions under which HBO becomes effective in favorably affecting wound outcomes [51]. A personalized approach may need to be established based on achieved a specific wound tissue oxygen tension level as opposed to using the same regimen for all patients.

Stromal-Derived Factor-1α and EPC Homing

Hyperoxia stimulates progenitor cell release from the BM, but these cells can only effectively be recruited to wounds to enhance vasculogenesis and healing if the cytokine milieu in the cutaneous wound bed is optimized [4, 44, 55]. In other words, in addition to mobilization from the BM, EPCs must undergo proper homing in order to reach the target tissue and bring about neovascularization. EPC homing includes rolling in blood vessels at target tissue, adhesion to the endothelial cell monolayers lining on the vessel wall, transendothelial migration, and incorporation into new vessels [2]. Similar to leukocyte recruitment during inflammation, EPCs use adhesion molecules for homing to sites of neovascularization. Chemokines play a critical role in this regulation. Stromal cell-derived factor (SDF)-1α is the predominant chemokine that mediates migration and homing of stem/progenitor cells through its receptor CXCR4 on the EPC [3], which can be induced by stress and injury [14]. EPC recruitment and trafficking at the tissue level is directed by ischemia-induced upregulation of SDF-1α, which acts as a signal guiding EPCs into areas of ischemia [3, 56, 57]. Inhibition of the SDF-1α/CXCR4 axis partially blocks homing of stem/progenitor cells to the ischemia myocardium [58], ischemic wounds, as well as prevent their adhesion to endothelial cell monolayers in vitro [56].

Gallagher et al. recently demonstrated that local concentration of SDF-1α in the diabetic wound tissue is significantly decreased, with

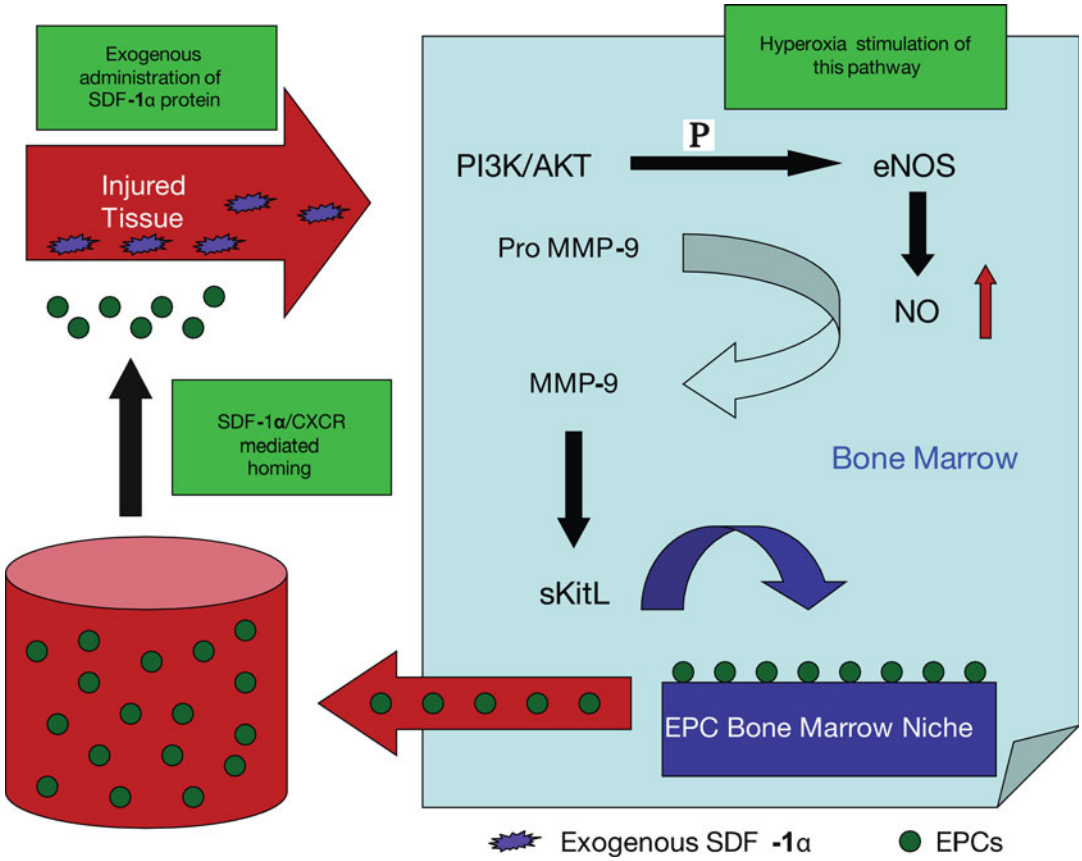

Fig. 12.4 Hyperoxia has been shown to increases BM NO levels via an eNOS-mediated pathway, which in turn triggers EPC mobilization into circulation in both nondiabetic mice and nondiabetic humans. In addition, exogenous administration SDF-1α recombinant protein increases homing of EPCs to the wound, as demonstrated by increased wound numbers of EPCs. In addition, not only does supplementation of exogenous SDF-1α increase wound-level EPC recruitment, but when used concomitantly with HBO, it also synergistically increases circulating EPCs in diabetic mice. BM transplantation experiments have further demonstrated that SDF-1α enhances EPC homing in diabetic cutaneous wounds

fewer number of baseline cells staining positive for SDF-1α [55], which could be responsible for the impaired homing of BM-derived EPCs in diabetes. SDF-1α is decreased approximately 50% in wounds of streptozocin-induced diabetic mice [14]. Epithelial cells and myofibroblasts appear to be mainly responsible for this down-regulation [14]. These impairments can be therapeutically addressed by improving the cytokine milieu. One option is by injecting exogenous SDF-1α protein into diabetic wounds. It has been demonstrated not only that supplementation of exogenous administration of SDF-1α to wounds of diabetic mice increases wound-level EPC recruitment, but also when used concomitantly with HBO; it synergistically increases circulating EPCs in diabetic mice [14]. Hence, SDF-1α can regulate both EPC mobilization and recruitment, though the molecular mechanisms remain unclear. The combination of HBO and SDF-1α resulted in a 11-fold increase in circulating EPCs, compared to the fourfold increase and twofold increase for HBO and SDF-1α alone, respectively [14]. The cytokine milieu of the wound granulation tissue may lead to additional paracrine effects from factors released by the wound that at a systemic level further enhance BM EPC release [14]. Together with hyperoxia, these local factors greatly increase systemic mobilization of EPCs (Fig. 12.4).

BM transplantation experiments have further demonstrated that SDF-1α enhances EPC homing in diabetic cutaneous wounds. Wounds were created on streptozocin-induced chimeric mice, which were reconstituted by transplanting BM cells from GFP transgenic mice after gamma-radiation. A synergistic fivefold increase in the number of EPCs was observed in wound tissue of diabetic mice treated with both HBO and SDF-1α [14]. Also, wound closure rates in the mice that received HBO and daily wound injections of SDF-1α were the fastest when compared to mice that only received one therapy, correlating with highest blood vessel density, stromagenesis, and collagen deposition [14]. Therefore, in addition to increasing the release of BM EPCs, HBO and exogenous recombinant SDF-1α protein in the wound synergistically enhances EPC recruitment to wound tissues and improves wound healing in diabetic mice [14]. The cells that are released from the BM are homed to the cutaneous wounds by these chemokines, thus hand in hand improving wound healing in diabetes [3].

The need for new modalities of treatment for recalcitrant diabetic foot ulcers has spurred the advent of molecular therapeutics and growth factors. While SDF-1α is still in the preclinical investigational period, other growth factors, such as VEGF, platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF), have been studied in the clinical setting to determine their wound healing potential [59–63]. The reasoning to examine the efficacy of these molecules stems from the increased oxidative stress in cell types susceptible to hyperglycemia, such as fibroblasts and macrophages, which subsequently display dysfunctional expression and responses to growth factors and cytokines in the setting of diabetes [64]. Chronic oxidative stress induced by hyperglycemia may also induce these cells to become senescent and growth factor therapy may rescue these cells and activate them to enter the cell cycle [64].

Topical recombinant human VEGF (rhVEGF) has been studied in *db/db* mice and it significantly accelerates wound healing and increases neovascularization in the wound bed [65]. It induces upregulation of PDGF-B and fibroblast growth factor-2 in treated wounds, and topical VEGF treatment increases recruitment of bone marrow-derived endothelial lineage cells to the wound [65]. Despite its success in mice, however, rhVEGF in humans demonstrates positive trends suggesting improved healing though further studies are required to characterize efficacy more completely [60]. Human recombinant basic fibroblast growth factor (bFGF) was also studied in a pilot, randomized, double-blind trial for 6 weeks of inpatient treatment and 12 weeks of outpatient follow-up, but no advantage over placebo was found in the group who received topical bFGF [61]. Randomized controlled trials have also been conducted to study the effect of G-CSF, and it was found that adding G-CSF to the care of chronic diabetic wounds did not significantly affect the likelihood of resolution of infection or wound healing, but it was associated with significantly reduced chances of surgical interventions, such as amputations [66].

Numerous multicenter double-blind placebo-controlled trials have been conducted to study the effectiveness of topical recombinant human PDGF-BB (rhPDGF-BB, becalplermin) in conjunction with standardized regimen of good wound care at healing chronic diabetic ulcers [59, 62]. Becaplermin gel 100 μg/g, in conjunction with good wound care, significantly increased the incidence of complete wound closure and reduced the time to complete closure of chronic diabetic neuropathic ulcers [59, 62]. In addition, the incidence of ulcer recurrence 3 months after healing was the same in all treatment groups, showing that the durability of these healed wounds were comparable [62]. More recently in 2006, another randomized, prospective, blinded clinical trial found the topical PDGF. When compared placebo gel for 20 week treatment period, brought about significant increase in complete healing, and decreased time to complete healing by 30% [63]. Becaplermin is the only growth factor approved by the US FDA for use in diabetic forefoot ulcers. It is indicated for uninfected diabetic foot ulcers that have an adequate vascular supply. These successes have not transferred to the clinical setting, as the efficacy is not clear and the drug is not widely used. Further work is

necessary to clarify the use of becaplermin in everyday clinical practice, and further research is needed to assess the potential room for improvement of becaplermin as well as other growth factors [67]. Along the same lines, the success of growth factor therapy in general is intimately dependent on proper ulcer care [64].

Financial analyses performed to study the cost-effectiveness of these recombinant products have found that due to the shorter treatment periods (higher healing rates), fewer complications (infections and gangrene that subsequently leads to amputation), and fewer impatient episodes the initial cost of the novel biotechnology products may be offset, making the treatment cost-effective and at times cost-saving [68]. The use of these products should be limited to wounds that are unresponsive to conventional methods of healing.

Due to complexity and variety of growth factors that are involved in the process of wound healing, it is likely that the use of one particular growth factor is not enough to bring about effective wound healing. Therefore, the combination of multiple therapeutic strategies perhaps the combinations of chemokine, such as SDF-1α, and a growth factor will result in greater healing rates in the affected patients.

Conclusion

Diabetic lower extremity and foot ulcers affect a large portion of the population and it is imperative that an effective therapeutic approach be determined as it remains the number one cause of lower extremity amputations and causes a high rate of morbidity and mortality in afflicted patients. The economic burden of diabetic foot ulcers come from high recurrence rates of ulcers, even after amputation, complex multimodality treatments that involve different teams of doctors, especially for patients with osteomyelitis [68].

The care of diabetic foot ulcers should encompass a multidisciplinary approach.

In addition to the traditional treatment methods of chronic diabetic ulcers, novel molecular methods that optimize neovascularization in these wounds represent new targets of therapy. As discussed above, the correction of impaired local angiogenesis has proven to be critical in the development of therapeutic protocols for chronic diabetic wounds. Hyperoxia has demonstrated to increase mobilization of EPCs from their bone marrow niche. HBO is not invasive, has few side effects, and has been applied with varying degrees of success in chronic diabetic wounds. Other alternatives methods of treatment targeting the eNOS-NO pathway could further enhance HBO's effect. It is also imperative to fine-tune the homing process of BM progenitor cells to the periphery in order to synergistically improve wound healing. Although some growth factors have been approved for the treatment of chronic foot ulcers, their efficacy has yet to be proven on a widespread level.

Another method of increasing progenitor cells in the wound is to deliver these progenitor cells that have the ability to differentiate into different cell types and produce various cytokines and growth factors directly to the wound [69]. Animal studies have shown that diabetic wounds treated with lineage-negative progenitor cells demonstrate a decreased time to closure, and vascular density are significantly higher in wounds treated with lineage-negative progenitor cells [8]. Lin et al. also showed that topically applied lineage-negative progenitor cells were incorporated into the wound, and they differentiate into vascular structures, bringing about neovascularization [8]. In addition to lineage-negative progenitor cells, adipose tissue-derived stromal cells, which have similar ability to undergo multilineage differentiation, can improve granulation tissue formation, increase capillary formation, and increased epithelialization of wounds in diabetic mice [11].

Studies in rats have also demonstrated similar findings: Kwon et al. and McFarlin et al. showed that topically and systemically administered bone marrow-derived mesenchymal stem cells (MSCs) promote healing of facial wounds in diabetic rats, as demonstrated by increased neovascularization, increased collagen levels in the wound bed, and increased expression of growth factors critical to proper repair an regeneration of damages tissues [10]. In addition, MSCs that were systemically administered engrafted to the wound [10].

Studies in human subjects have also shown that local transplantation of autologous bone marrow cells increases leg perfusion and reduces amputation in patients with advanced critical limb ischemia[9,12].Bonemarrowcellauto-transplantation results in increased ankle-brachial index (ABI) and transcutaneous oxygen tension, as well as decreased analgesic consumption and improved walking distance [9].

EPC is another cell type that has been moved from experimental models to clinical trial. It has been tested in acute and chronic ischemia heart disease, and outcomes are encouraging [70, 71]. Many properties of EPCs make them ideal candidates for cell-based therapy for ischemic disorders. For example, they are endogenous and BM-derived, and able to mobilize from the BM and home to various peripheral sites. In addition, they are relatively stable in lineage speciation in vitro, which allows for genetic and epigenetic manipulation [2]. The Restore-CLI trial is a prospective randomized double-blinded controlled multicenter trial that studies megadoses of BM stem and progenitor cells on ischemic wound healing. These megadoses of cells are shown as tissue regeneration cells (TRCs) or vascular repair cells (VRCs), and they differentiate into various lineages after being injected into human subjects. Patients and physicians are blinded for both the treatment injections as well as for follow-up visits. The Restore-CLI trial is currently in Phase IIb of its development [72]. It is likely that both hematopoietic stem cells, such as EPCs and MSCs, are both necessary to bring about full healing of wounds, as neovascularization as well as stromal deposition are both necessary to bring about strong granulation tissue formation. The efficacy of cell-based therapies to augment neovascularization and healing can further be increased by improved recruitment to the target site. The development of a safe and effective method of delivering SDF-1α and/or other chemokines into the wound will further help to ensure that EPCs mobilized from the bone marrow will in fact reach the injured tissue. Furthermore, combining the use of exogenous SDF-1α with HBO and/or TRCs could synergistically influence EPC effects by targeting both homing and mobilization steps.

In summary, our current knowledge of EPC mobilization and homing in the diabetic murine model include the existence of impaired eNOS phosphorylation in the BM and decreased expression of SDF-1α in the granulation tissue of cutaneous wounds. These phenomena have direct impact on BM EPC mobilization and homing respectively, and can be therapeutically altered by HBO and exogenous administration of SDF-1α. These two modalities of treatment will synergistically increase wound levels of EPCs, promote neovascularization and improve wound healing, which carries important clinical potential. A better understanding of the molecular and cellular etiologies of chronic diabetic wounds in combination with the development of effective approaches for correcting EPC deficits and functional impairments will eventually result in the development of clinical therapies that prevent wound progression, eliminate amputations, and promote rapid healing in these patients. This combination with good wound care, including debridement to remove nonviable tissues, will bring about faster healing of these recalcitrant wounds.

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Part III

Management of the Diabetic Foot

Wound Bed Preparation of the Diabetic Foot Ulcer

13

Vincent Falanga and Satori Iwamoto

Abstract

Over the last few years, substantial advances have been made in our understanding of the pathophysiology of diabetic foot ulcers, the importance of thorough surgical debridement, and how this standard therapeutic modality impacts on wound bed preparation (WBP). Importantly, the concept of WBP is revolutionizing the way we approach nonhealing or difficult to heal wounds, including those due to diabetes. Much of what we do clinically, from elimination of bacterial burden, to debridement, and to the use of new technologies to heal diabetic foot ulcers, can now be seen as being part of the comprehensive WBP strategy and as facilitating the process of healing [Falanga Wound Repair Regen 8:347–52, 2000; Falanga et al. Ostomy Wound Manage Suppl:2–13, 2008]. From a therapeutic standpoint, at least in the USA, large multicenter clinical trials have led to the regulatory approval for neuropathic diabetic ulcers of topically applied platelet-derived growth factor (PDGF) BB (beclapermin or Regranex, Ortho-McNeil, Raritan, NJ) (Smiell et al. Wound Repair Regen. 7:335–46, 1999; Steed J Vasc Surg 21:71–8, 1995; Steed et al. J Am Coll Surg 183:61–4, 1996) and living bioengineered skin [Apligraf, Organogenesis, Canton, MA (Falanga Lancet 366:1736–43, 2005; Lazic and Falanga Plast Reconstr Surg 127 Suppl 1:75S–90, 2011; Veves Plast Reconstr Surg 127 Suppl 1:91S–2, 2011; Veves et al. Diabetes Care 24:290–5, 2001); and

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Dermagraft, Advanced Biohealing, La Jolla, CA (Marston et al. Diabetes Care 26:1701–5, 2003)], and have dramatically increased the number of available therapeutic options. However, not to be forgotten are advances that these and other clinical trials have brought to the standard of care for treating neuropathic diabetic foot ulcers. Indeed, these improvements in standards of care for diabetic foot ulcers have raised the bar for proving the effectiveness of new treatments. Stated differently, it may have become harder to prove the effectiveness of new therapeutic agents. Thus, from now on we may be looking for "quantum" jumps in therapeutic efficacy in the treatment of diabetic foot ulcers.

Keywords

Debridement • Wound bed preparation • Pathophysiological factors • Negative pressure • Impaired blood flow • Hypoxia • Pathophysiological status • Phenotypic alteration • Critical paradigm • Diabetic foot ulcer • Therapeutic advances • Bioengineered skin • Gene therapy • Stem cells • Progenitor cells

Introduction

Over the last few years, substantial advances have been made in our understanding of the pathophysiology of diabetic foot ulcers, the importance of thorough surgical debridement, and how this standard therapeutic modality impacts on wound bed preparation (WBP). Importantly, the concept of WBP is revolutionizing the way we approach nonhealing or difficult to heal wounds, including those due to diabetes. Much of what we do clinically, from elimination of bacterial burden, to debridement, and to the use of new technologies to heal diabetic foot ulcers, can now be seen as being part of the comprehensive WBP strategy and as facilitating the process of healing [1, 2]. From a therapeutic standpoint, at least in the USA, large multicenter clinical trials have led to the regulatory approval for neuropathic diabetic ulcers of topically applied platelet-derived growth factor (PDGF) BB (beclapermin or Regranex, Ortho-McNeil, Raritan, NJ) [3–5] and living bioengineered skin (Apligraf, Organogenesis, Canton, MA [6–9]; and Dermagraft, Advanced Biohealing, La Jolla, CA [10]), and have dramatically increased the number of available therapeutic options. However, not to be forgotten are advances that these and other clinical trials have brought to the standard of care for treating neuropathic diabetic foot ulcers. Indeed, these improvements in standards of care for diabetic foot ulcers have raised the bar for proving the effectiveness of new treatments. Stated differently, it may have become harder to prove the effectiveness of new therapeutic agents. Thus, from now on we may be looking for "quantum" jumps in therapeutic efficacy in the treatment of diabetic foot ulcers.

The aim of this review is to examine certain basic science factors involved in the development of diabetic foot ulcers, critical therapeutic advances, such as topically applied PDGF (beclapermin or Regranex) and dermal (Dermagraft) or bilayered (Apligraf) bioengineered skin, and to discuss these topics in the context of WBP (see below). We focus on the role of debridement, how it affects WBP, and how the two are intimately linked. Advances in smart dressings, in negative pressure devices, and in the use of gene therapy and stem/progenitor cells are also highlighted within the same context of WBP.

Overview of Debridement and Wound Bed Preparation

It was always assumed that clinicians would uniformly perform surgical debridement as part of a unified approach to the care of chronic wounds. However, this assumption may have been wrong, and the meaning of debridement was variable among clinicians. The thorough extent of debridement that is required, too, did not always reflect the reality of office practice and clinical trials. This is not to say that competent clinicians did not perform debridement of eschars and frankly necrotic tissue in compromised diabetic foot ulcers. However, it has become increasingly clear that regular debridement, to remove the callus surrounding the wound and the fibrinous wound bed (not necessarily frankly necrotic tissue), may not have been widely practiced [4, 5]. We have referred to this more thorough and regular approach as "maintenance debridement" for diabetic foot ulcers, still within the context of WBP [1, 2, 11, 12]. Figure 13.1 outlines this important strategy that is inherent to WBP [2]. In the case of diabetic foot ulcers and as shown in Fig. 13.1, it is critical that the extent of tissue necrosis or possibility of abscess formation be found at the

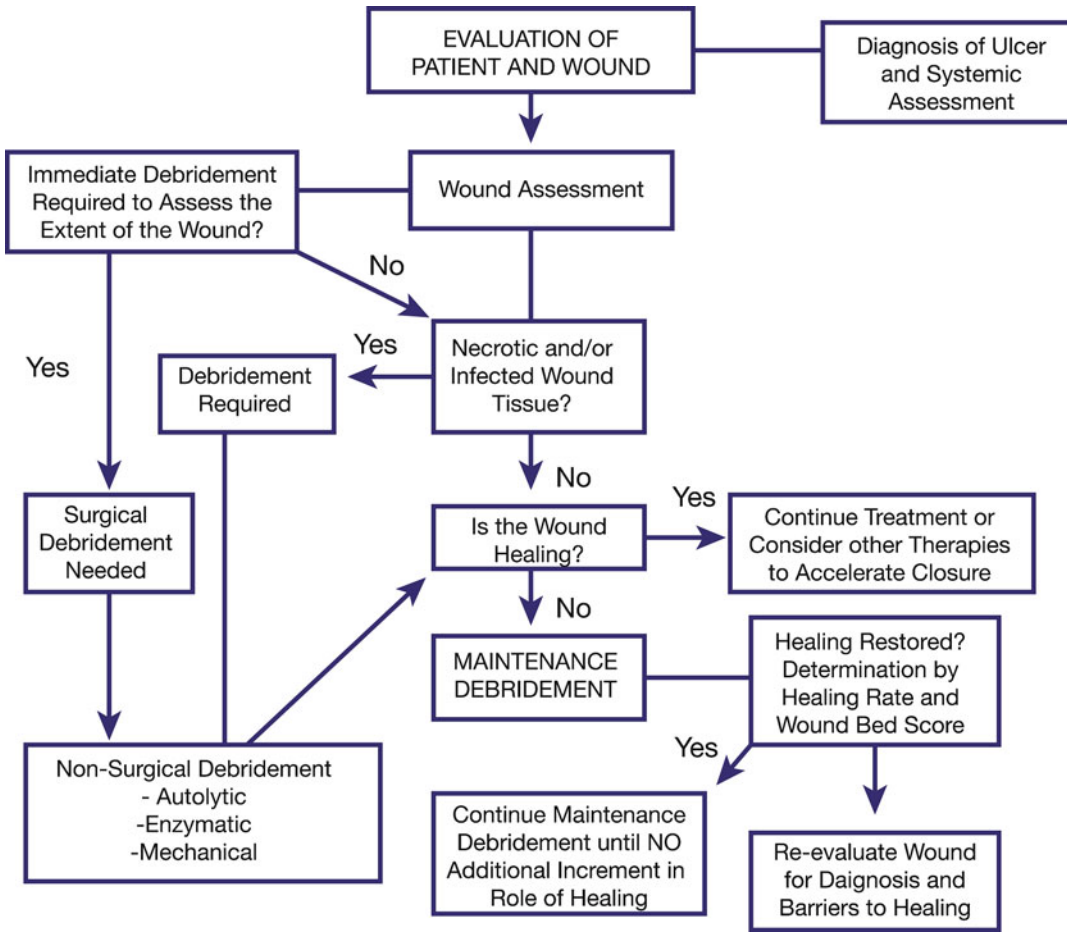

Fig. 13.1 Diagrammatic representation of maintenance debridement during wound bed preparation. Evaluation of the patient and the extent of tissue necrosis, as well as the possibility of infection/abscess, are critical in the initial phases. Surgical debridement is likely most appropriate for this initial phase in patients with diabetic foot ulcers. As indicated in the figure, it might be necessary to continue to debride the wound when healing is still not taking place, even in the absence of obvious clinical findings of tissue necrosis (copyrighted, Falanga 2008)

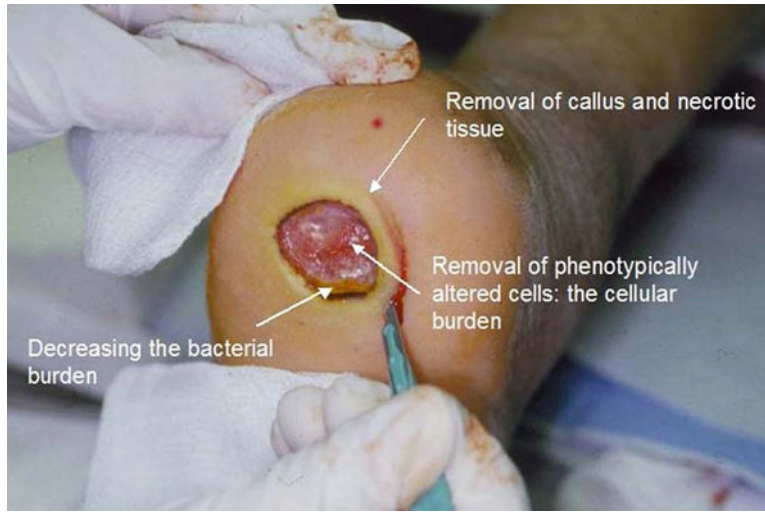

Fig. 13.2 Clinical photograph showing surgical debridement of the callus and wound bed in a diabetic neuropathic foot ulcer. The photograph also indicates how the surgical debridement may remove the necrotic tissue, bacterial burden and, possibly, phenotypically altered cells that may interfere with healing (copyrighted, Falanga 2003)

initial evaluation. Anyhow, to what extent not following this "standard of care" or debridement may have played a role in the apparent failure of certain therapeutic products tested in the past is unclear. The initial pilot study of topically applied PDGF helped change the way we conduct clinical trials for diabetic foot ulcers. Indeed, the effectiveness of PDGF in those trials seems to have been highly dependent on concomitant and thorough regular use of surgical debridement, and actually worked synergistically with it [4, 5]. This important relationship between debridement and efficacy of an advanced therapeutic product has been discussed elsewhere, and is part of this review in the way it affects the way we view WBP. It should be noted here that subsequent trials in diabetic ulcers adopted regular debridement of the wound bed and callus (Fig. 13.2), to the point that, indeed, an aggressive approach to debridement (Fig. 13.1) is now considered the standard of care, as long as the wound is properly vascularized. In this review, we discuss certain abnormalities involved in the pathogenesis of diabetic foot ulcers and their failure to heal, and which have a great impact on WBP. Traditionally, these cellular and molecular abnormalities have been wrongly considered separately from the clinical approach, with debridement being seen mostly as a mundane clinical procedure to remove dead tissue. However, as we shall see, close interactions are emerging between molecular events and certain critical aspects of wound care. WBP is a unifying concept that embodies many of these interactions. Figure 13.2 illustrates examples of this important concept.

Clarifying the Concept of Wound Bed Preparation

The concept of WBP was designed to help clinicians take into consideration all of the various, and often interrelated, deficiencies of a nonhealing wound [1, 11]. Over the years, the interpretation of WBP and its ramifications have been refined [2, 13]. However, one particular clarification of this concept is in order: The comprehensive approach to WBP was meant to be an immediate and integrated correction (rather than a sequential correction) of all of the wound bed deficiencies. This is crucial in the care of diabetic foot wounds. There has been a subtle corruption of this concept in recent years, and that needs to be corrected.

In spite of the initial emphasis on an integrated approach to WBP, some clinicians may have interpreted each of the wound bed deficiencies to be in

isolation and, therefore, may have approached WBP in a sequential manner, correcting one deficiency after another. For example, after managing the fundamental abnormalities in a diabetic patient (i.e., neuropathy, excessive pressure on the structurally abnormal foot, edema, inadequate arterial supply, hyperglycemia, poor nutrition, etc.), clinicians would often find themselves confronted with a long list of deficiencies of the wound bed. The clinicians would then try to correct each deficiency of the wound bed one after another, in a sequential fashion. Thus, they would first remove necrotic or altered tissue; they would then decrease the bacterial burden and reduce excess exudate; and finally, they would ensure the presence of cells within the wound which can regenerate the wound bed tissue. With a seemingly overwhelming list of wound bed deficiencies to correct, it may not be surprising to find some clinicians who have misinterpreted WBP as a checklist of wound bed deficiencies to be corrected one at a time, or at least not all at once.

To make matters a bit more confusing, one development may have deepened this misconception. In 2003, a helpful mnemonic was introduced to help clinicians remember the fundamentals of WBP. Introduced as the "TIME concept" [13, 14], TIME is an acronym for Tissue (nonviable or deficient), Infection/inflammation, Moisture imbalance, and Edge of wound. It was hoped that TIME would help as a mnemonic for WBP but the authors, as for example one of us (VF), may have failed to predict the subsequent misinterpretation of the concept of TIME by clinicians caring for nonhealing diabetic ulcers.

Although it is true that TIME is a helpful mnemonic, it may however have erroneously suggested that wound bed deficiency could be dealt with separately and in sequence, rather than all together and immediately. Furthermore, in an unfortunate way the word TIME may have wrongly suggested that wounds could be allowed to have considerable "time" to heal or that the therapeutic steps required time. Finally, in our opinion, it has become clear that clinicians may have delayed using advanced therapies until they had "fully prepared" the wound bed. As a result, the WBP concept as first developed [1] may have undergone some modifications that did not always point to the need for immediate action to correct the wound bed abnormalities.

Realistically, especially when it comes to diabetic foot wounds, there is little time to lose [2]. It can be a matter of days, weeks (sometimes even hours) before diabetic foot wounds progress to the point where the diabetic foot or the limb may become unsalvageable and even require amputation. Thorough assessment of the extent of the wound, and certainly the exclusion of an underlying abscess or sinus tracts must be immediate (Fig. 13.1). Therefore, while definitely not disregarding the concept of TIME as a helpful mnemonic, we wish to clarify the concept of WBP as follows. First, diabetic wound bed abnormalities are to be recognized early and treated immediately. Second, the various abnormalities of the wound bed are to be corrected/improved in an integrated fashion, rather than one at a time. Third, advanced therapies may need to be introduced at early stages; advanced therapies (such as growth factors, bioengineered skin, and more recently stem cells) prepare many components of the wound bed in an integrated fashion. In fact, although a retrospective analysis, a rather recent study has reaffirmed the importance of the early use of advanced therapies [15]. We consider advanced therapies in the subsequent sections.

Overview of Diabetic Foot Ulcers and Pathophysiologic Principles

Recent publications provide reviews of diabetic ulcers, their basic pathophysiology, and appropriate treatments [16–21]. Besides arterial insufficiency, neuropathy plays a major role in the development of ulceration in diabetic patients. It is important to realize that our concepts of pathophysiology have important consequences on treatment. For example, for decades it was thought that the main problem in diabetes was "small vessel disease," a rather poorly defined term that was offered as an explanation for many of the complications of this metabolic disease, including foot ulcers. It is likely that much needed surgical revascularizing procedures were not performed

because of the notion of "small vessel disease," at least as the latter was being interpreted. Therefore, the realization a few years ago that the concept of a truly occlusive microangiopathy in the lower extremities of diabetic patients is incorrect or not specific for diabetic patients has brought about a dramatic benefit in how revascularization of the diabetic foot is viewed and more actively pursued [22].

Particularly in the context of diabetic ulcers, clinicians and scientists in the past have talked about "failure to heal" [23]. However, this term does not accurately describe what is observed clinically, and it may be preferable to use the term "impaired healing." The fact is that many chronic wounds, including those due to diabetic complications, do heal in an appropriate time frame when the underlying basic pathophysiology is optimally addressed. For example, with uncomplicated (i.e., without infection or significant arterial insufficiency) diabetic neuropathic foot ulcers, healing should occur relatively unimpeded once off-loading is appropriately instituted to relieve pressure [24]. However, prospective studies are required to answer the question of whether relatively simple but time-consuming measures, such as contact casting, can greatly improve ulcer healing. There is published evidence that contact casting may indeed be effective [24, 25], but additional studies are needed to evaluate the performance of contact casts in larger or deeper ulcers. There are also multiple methods for off-loading using a contact cast approach [21, 26–28].

A typical feature of diabetic ulcers is their propensity to become heavily colonized with bacterial and, less commonly, fungal organisms. These infectious agents may play a major role in impaired healing. Bacterial colonization has also been called bioburden or bacterial burden. Questions remain about what constitutes an unacceptable level of organisms in the affected tissues and the level of bioburden that would disrupt the healing process. This has been discussed extensively in other publications [2, 13, 29]. However, evidence has been developed that the bacterial species present in the wound bed may not as critical for impaired healing as a level greater than or equal to 10 [6] total organisms per gram of tissue. In practical terms, it makes theoretic and clinical sense to decrease the bacterial burden of wounds. Nevertheless, we know very little about the mechanisms underlying impaired healing in the presence of large number of organisms. More recently, there has been increasing interest in the possible presence of biofilms in chronic wounds and their role in impaired healing or even ulcer recurrence. Biofilms represent bacterial colonies surrounded by a protective coat of polysaccharides; such colonies become more easily resistant to the action of antimicrobials and the bacteria seem to "communicate" their status by a process called "quorum sensing" [30–32]. At the moment, there is no hard evidence for what role biofilms play in diabetic foot ulcers. Debridement can remove the bacterial burden and "reset" the diabetic foot ulcer to a mode that is more conducive to healing (Fig. 13.2).

Other Pathophysiological Factors Interacting with Debridement and Wound Bed Preparation

Growth Factor "Trapping"

Debridement has other important impacts on basic pathophysiological abnormalities. Thus, removing the callus around the diabetic foot ulcer and the fibrinous wound bed can have beneficial consequences on growth factor availability. The concept of growth factor trapping was first developed in the context of venous ulcers [33], but has applicability to a variety of chronic wounds, including diabetic neuropathic foot ulcers. The hypothesis is that certain macromolecules and even growth factors are bound or "trapped" in the tissues, which could result in unavailability or maldistribution of critical mediators, including cytokines [33–35]. Even topically applied growth factors can suffer the same fate of becoming bound to leaked macromolecules and altered matrix components. Trapping of growth factors and cytokines, as well as matrix material, however limited, has the potential to cause a cascade of pathogenic abnormalities. For example, in the well-coordinated process of wound healing,

disruption of some key mediators could have adverse consequences well downstream. Binding of growth factors by macromolecules that leak into the dermis, such as albumin, fibrinogen, and α-2-macroglobulin, may disrupt the healing process. Alpha-2-macroglobulin is an established scavenger for growth factors. There is also evidence that transforming growth factor-β1 (TGF-β1), a critical multifunctional polypeptide, is bound within the pericapillary fibrin cuffs in the dermis [33, 34, 36].

Wound Fluid and Moist Wound Healing: The Promise of "Smart" Dressings

The bacterial burden and the inflammatory process developing in diabetic foot ulcers alter the balance between appropriate moisture levels in the wound, extracellular matrix deposition and remodeling, and the levels of tissue matrix metalloproteinases (MMPs). A major breakthrough of the last 50 years, in terms of how we manage wounds, was the experimental evidence developed by George Winter indicating that reepithelialization is accelerated when wounds are kept moist [37]. This advance has led to the development of a vast array of moisture-retentive dressings that promote "moist wound healing" [38, 39]. The experimental evidence for moist wound healing was mainly developed in acute wounds, and its lessons were quickly extrapolated to chronic wounds. Contrary to what had always been conventional wisdom, keeping the wound moist has not resulted in increased infection rates [40–42]. However, the possibility that occlusion leads to infection remains a fear of many clinicians. It is not entirely clear whether moisture-retentive dressings work mainly by keeping the wound fluid in contact with the wound. One of the reasons for this uncertainty is that wound fluid appears to have distinctly different properties in acute and chronic wounds. For example, it has been shown that fluid collected from acute wounds will stimulate the in vitro proliferation of fibroblasts, keratinocytes, and endothelial cells [43–45]. Conversely, fluid obtained from chronic wounds will block cellular proliferation and angiogenesis [46] and contains excessive amounts of MMPs capable of breaking down critical extracellular matrix proteins, including fibronectin and vitronectin [47–49].

Dressings are fundamental to wound bed care and they are directly linked to the issue of moisture balance in the wound bed. Recently, technological advances have allowed dressings to monitor the wound bed and to respond accordingly. These technologically advanced dressings have been termed "smart dressings" [50, 51]. Such dressings address different aspects of WBP, including bacterial control, MMPs control, debridement, and moisture control. However, most of these smart dressings are still in their investigational stages and therefore address only one component of WBP at a time. At least four types of smart dressings have been reported, each type addressing a different deficiency of the wound bed. It is unfortunate that their commercial development has not proceeded quickly, but it is useful to consider their properties and how they could ultimately benefit WBP. One type of dressing focuses on bacteria in the wound bed by responding to bacterial products. For example, proteinases found in the presence of certain bacteria are used to cleave synthetic linkers in the dressing which, in turn, allow the release of antibiotics [52, 53]. More recently, other investigators have created vesicles that rupture in response to bacterial virulence factors, thereby leading to the release of antibiotics [54]. A second type of smart dressings regulates signaling molecules in the wound bed. For example, a microsphere that releases its contents only in the presence of MMPs has been designed as a way to control levels of MMPs [55]. A third type of smart dressing debrides necrotic material based on technology utilizing a silicone-based dressing that releases a subtilisin protease in response to moisture [56]. A fourth type of smart dressing optimizes moisture levels in the wound bed by removing excess fluid. These latter dressings respond to the amount of wound exudate and adjust the moisture permeability of the dressing [57, 58]. A small prospective randomized study of a prototypic moisture-controlling smart dressing was found to improve the healing of diabetic foot ulcers [59]. Thus, the four types of smart dressings described

as examples hold promise in responding ("smartly" from the engineering standpoint) to the wound bed microenvironment and providing a potentially more direct approach to WBP, whether it be infection control, MMPs modulation, removal of necrotic burden, or moisture balance and control.

Still, even with the development of the smart dressings just described, challenges would remain because these dressings may not be able to address all the needs required in WBP. For example, among the dressings we have just described, the smart dressing that controls infection does not control exudate. Furthermore, the amplitudes of the responses are limited. Finally, because most smart dressings are still in their investigational stages, there are as yet no studies showing that they are more effective than standard dressings, such as traditional films, hydrocolloids, foams, gels, or antimicrobial slow-release wound dressings. Actually, the latter dressings, which are already available, can already be classified as "smart" in that they respond to the wound bed microenvironment by matching the release of the antimicrobial agent with the moisture level; they also eliminate or diminish necrotic or nonviable tissue. Therefore, if smart, more specific dressings are to be useful for WBP in the future, WBP would have to be accompanied by more sophisticated ways to measure bacteria, MMPs, cytokines, etc. We believe this more informed way to measure the characteristics of the wound bed will take place.

More on MMPs in the Context of WBP

MMPs are vital for wound healing, and not surprisingly offer the promise that we can manipulate their levels and/or activity to effect better WBP. Their name, MMPs, derives in part from their role in degrading proteins of the extracellular matrix and in part from the presence of a metal ion (Zn^{2+} or Ca^{2+}) at the active site. There are at least 24 mammalian MMPs [60]. MMPs play a vital role in normal wound healing. In general, excess levels of MMPs are associated with abnormal healing in diabetic wounds [61]. Therefore, one approach to preparing the diabetic wound bed is to control the levels of MMPs.

An insight into abnormal MMPs levels in the diabetic wound bed can be gained by first considering the role of MMPs in normal wound healing. An important role of MMPs is to degrade components of extracellular matrix needed for cellular movement. These enzymes degrade the matrix to allow the epithelium to resurface the wound, and they also break down the extracellular matrix to allow scar remodeling and a decrease in fibrosis. After they are secreted by myofibroblasts, MMPs help contract wounds and regulate inflammation. In support of these various roles of MMPs in tissue repair, normal wound healing was found to be delayed when the levels of MMPs were reduced by the MMP inhibitor BB-94. This delay was caused by the inhibition both of keratinocyte migration (which in turn prevented myofibroblast formation) and of TGF-β1 [62]. The number of known MMPs keeps growing, but of the 24 recently recognized mammalian MMPs [60], some act in various ways during wound healing. Studies with MMP-8 deficient mice have shown that MMP-8 is important in the control of inflammation and that its absence may delay wound healing [63]. Studies on MMP-9 revealed its critical role in epithelialization, remodeling, and the inflammatory response. Levels of MMPs are also controlled by the so-called inhibitors of MMPs (or TIMPs for short) which help control levels of MMPs [60]. Thus, MMPs are critical to normal wound healing and an imbalance (excessively low or high levels) of MMPs may lead to impaired healing.

In diabetic wounds, there is an imbalance of MMPs. The exaggerated inflammatory reaction in diabetic wounds can in itself cause an increase in MMPs. In chronic diabetic foot ulcers, MMP-1, activated MMP-2, MMP-8, and MMP-9 were found to be overexpressed, while the tissue inhibitor of MMP, TIMP-2, was suppressed [64]. In another study of diabetic ulcers, it was found that high levels of MMP-9 were associated with poor healing [65]. Furthermore, experimental mouse studies have shown that high MMP-9 levels are associated with inadequate healing and, more

specifically, with decreased epithelialization [66]. In a clinical study of seven diabetic foot ulcers, high levels not only of MMP-9, but also of MMP-8 correlated with poor healing [67]. The same clinical trial also showed that delayed healing is associated with excessively high levels of MMPs, low levels of MMP-1, and a high level of TIMP-1 [67]. These findings point to the fine balance of MMPs needed for proper wound healing. It follows that ideal WBP may require not just the removal of excess levels of MMPs but, rather, an adjustment to optimal levels of specific MMPs.

Various approaches have focused on ways to control the levels of MMPs in diabetic wounds, some methods being less specific than others; this central issue of whether specificity is always required remains an important consideration in WBP. Inhibitors of wound healing are often found in wound exudate [68], and any method of exudate removal, whether by conventional dressings or by negative pressure devices, can theoretically be used to remove excess MMPs from the wound bed. A novel method of removing excessive levels of MMPs may be the use of either topically applied or systemically administered 17 β estradiol. The improvement in healing observed with the use of this estrogen may be due to reduction in the levels of MMP-2, MMP-13, and MMP-14 [69]. In addition, methods are being investigated not only to reduce MMPs, but also to adjust MMPs to optimal levels. For example, an MMP inhibitor, 2,3-dihydroxybenzoic acid, has been conjugated to microspheres to adjust the levels of MMP-2 and MMP-9 in diabetic wounds [70]. In another example, a dressing that incorporates an MMP cleavage site and responds only to the presence of MMPs [55] is another step toward adjusting levels of MMPs in more specific ways. Although new methods of directly adjusting levels of various MMPs are being developed, the most common method of doing so is by simply removing excess exudate by using simple dressings. However, as WBP becomes more sophisticated in the future, it will benefit from more precise approaches to help regulate MMPs in the wound bed. Again, the key will be to develop easy methods to measure and assess these and other key components of the wound bed.

Negative Pressure in WBP

As already mentioned, one might argue that the smart dressings we have discussed earlier may presently be too specific in that they address single components of the wound bed. Therefore, less specific and more global approaches are also being pursued. One such methodology involves the application of negative pressure to the wound bed. Several negative pressure devices are presently available. They have varied technical characteristics and ease of use, but they all share the concept that the wound bed can be improved by active and more aggressive removal of wound fluid and wound exudate. The technical use of negative pressure is relatively easy. Typically, the wound is covered with a semi-occlusive dressing, followed by a foam or gauze layer, on top of which an occlusive dressing with a suction tube is connected to an external vacuum source. The vacuum draws fluid through the foam/gauze and out of the suction tube.

Negative pressure devices/dressings may improve the diabetic wound bed through a variety of mechanisms, and not simply because of active removal of exudate. Some authors have argued that other beneficial effects include drawing the wound edges together, acting as a dressing to stabilize the wound microenvironment, decreasing edema, and creating microdeformities on the wound surface [71]. Other secondary effects of negative pressure are often cited but even more difficult to prove definitely. Such effects included a reduction in the bacterial burden, increased angiogenesis, and reduced amounts of MMPs. It is plausible to think that the removal of excess exudate may reduce the bacterial burden [72]. Presumably, alterations in the shape of the wound surface are not without biological consequences. The microdeformations may lead to an increase in angiogenesis as shown by histological increases in microvessel density in negative pressure-treated wounds [73]. Reduction of exudate may alter the levels of MMPs, as shown by zymographic evidence of reduction in MMP-9/NGAL, MMP-9, and MMP-2 (both latent and active) in negative pressure-treated wounds [73]. These secondary factors may provide optimal

conditions for the observed increase in granulation tissue in wounds to which negative pressure technology is applied [72, 73].

All of the effects of negative pressure for wounds, including both primary and secondary effects, suggest that negative pressure devices work in a multitude of ways to improve the wound bed. The critical test, however, is whether negative pressure shows efficacy in well-designed prospective clinical trials. Here, the field has not reached its full potential yet. Small studies of patients with diabetic foot ulcers have shown increased granulation and/or reduction in wound size in negative pressure-treated patients [74, 75]. There have been a few large randomized controlled studies. However, at least two systematic reviews of all randomized controlled studies conducted before 2008 concluded that negative pressure showed no clear benefit [76, 77]. Since 2008, there has been one randomized controlled trial with 342 patients (specifically with diabetic foot ulcers) that showed faster healing with no increase in complications compared to moist wound therapy [78]. In addition, it was reported that, when effective in diabetic patients with postamputation wounds, negative pressure was thought to be less costly than standard moist wound therapy [79] and just as safe [80]. However, more studies are needed to show true efficacy of negative pressure devices in chronic wounds and specifically in diabetic ulcers. It might be that the use of this technology has to be more fine-tuned, both in terms of how it is applied and which patients benefit the most. For example, the systematic and common use of negative pressure in many different types of wounds, without clear-cut clinical evidence of benefit, increases the overall wound care costs and makes it more difficult for governmental or private health care insurers to pay for the use of other advanced therapeutic agents.

However, despite this paucity of evidence-based studies on the efficacy of negative pressure, there are enough studies showing that the putative mechanisms (i.e., exudate decrease, bacterial load reduction, cellular proliferation increase, etc.) are actually taking place; they are likely helpful to WBP. One explanation for the paucity of large studies showing efficacy of negative pressure may be wound heterogeneity. Certain wounds may respond well, while others may not. For example, because it probably works primarily to reduce exudate, negative pressure may be more helpful in exudative wounds, such as deep (down to subcutaneous fat) diabetic wounds. Perhaps larger studies in which wounds are stratified on the basis of a wound bed score (WBS) [81] may show particular efficacy of negative pressure for certain subsets of diabetic wounds. Figure 13.3 shows a potentially useful WBS that can be used for such purpose [81]. The first letter of each clinical characteristic being assessed can be easily remembered because they sequentially lead to "wound bed." It should be noted that it is not possible to reliably score the wound bed as in Fig. 13.3 unless any amount of substantial exchar is either lifted or removed.

Impaired Blood Flow and Hypoxia

Of particular importance in diabetic ulcers is the level of oxygen tension at the wound site. Indeed, decisions about therapy with hyperbaric oxygen are based on demonstrable tissue hypoxia and the ability to overcome those low levels of tissue oxygen. In the case of ulcers due to poor tissue perfusion and consequent hypoxia, revascularization is required, also because chronic tissue hypoxia and necrosis are often accompanied by limb- and life-threatening infections that can lead to amputation. There is a substantial body of data indicating that low levels of oxygen tension as measured at the skin surface (transcutaneous oxygen measurements or $TcPO_2$) correlate with the inability to heal [82]. These data are most relevant in the treatment of diabetic ulcers, and can often guide therapy and even the level of amputation. However, it should be noted that ischemia is not the same as hypoxia. Interestingly, at least from a biological standpoint, hypoxia has been shown to have some stimulatory effects on wound cells, although the clinical relevance of these findings is not clear. Low levels of oxygen tension can stimulate fibroblast proliferation and clonal growth [83] and can actually enhance the transcription and synthesis of a number of growth

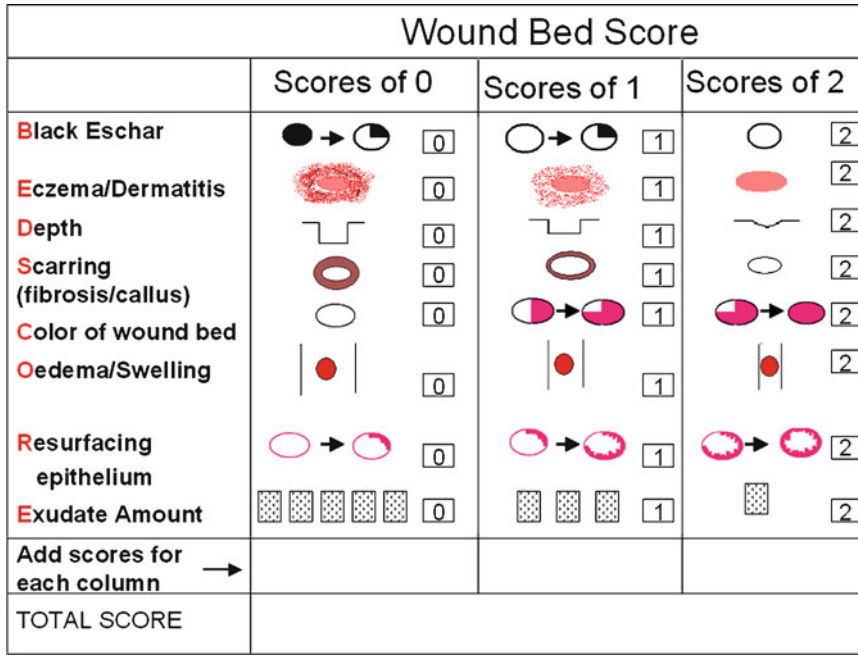

Fig. 13.3 The wound bed score (WBS) assigns a numeric whole number (0, 1, or 2) for assessment of wound bed preparation (WBP). A score of 2 for each of the eight clinical features (each corresponding to the letters in "bed score") is best, and a total added score of 16 is optimal. The following characteristics represent scores of 0, 1, and 2 points, respectively: percentage of black eschar present (>25%, 1–25%, 0%); severity of peri-ulcer eczema/dermatitis (severe, moderate, none, or mild); depth of the wound (severely depressed or raised compared to peri-wound skin); severity of scarring (severe, moderate, none, or minimal); percentage of pink-colored granulation tissue present (<50%, 51–75%, >75%); severity of edema/swelling (severe, moderate, none/mild); percentage of regenerating epithelium (healing edges) (<25%, 26–75%, >75%); severity of exudate/frequency of dressing changes (severe, moderate, none/mild). Any eschar must be lifted/removed for evaluating the wound bed and obtaining a WBS (copyrighted, Falanga 2007)

factors [84–86]. However, there is also evidence that exposure to hyperbaric oxygen can increase the production of VEGF [87]. It is still possible that low oxygen tension can serve as a potent initial stimulus after injury, such as surgical debridement, when it could possibly recruit circulating stem/progenitor cells or even epithelial stem cells at the edge of the wound [88].

Pathophysiological Status of the Wound and Phenotypic Alteration of Wound Cells

Figure 13.1 emphasizes the need for vigilance with regard to WBP and regularly performed debridement in diabetic ulcers. As shown in the left side of the diagram, in most cases and certainly when patients are first evaluated, surgical debridement is the best approach. Another critical relationship can be established between the value of maintenance debridement and the removal of resident wound cells that have become phenotypically abnormal. The normal process of wound repair goes through well-defined stages that are well studied [6]. However, chronic wounds do not seem to have defined time frames for healing. This is apparent both clinically and from the pathophysiological standpoint. It has been stated that the diabetic ulcers is "stuck" in the proliferative phase of wound repair. Indeed, there is evidence that the accumulation and remodeling of diabetic foot ulcers are impaired with respect to certain matrix proteins, including fibronectin [89–91]. There is also increasing evidence that the resident cells of chronic wounds

have undergone phenotypic changes that impair their capacity for proliferation and movement [89–91]. To what extent this is due to cellular senescence is unknown, but the response of diabetic ulcer fibroblasts to growth factors seems to be either impaired or requiring a sequence of growth factors. Similar observations have been made in other types of chronic wounds. For example, it has been reported that fibroblasts from venous and pressure ulcers are senescent, show diminished ability to proliferate [92–95], and that their decreased proliferative capacity correlates with failure to heal and lack of response to PDGF [96, 97]. There is also substantial evidence that ulcer fibroblasts are insensitive to the action of TGF-β1 and downstream peptides [98], and that this is the result of decreased receptor expression [99] and phosphorylation of key signaling proteins, including Smads and MAPK [100]. At the moment, it is not known whether this phenotypic abnormality of wound cells is only observed in vitro and whether it plays a role in impaired healing. Recent data also indicates that the development of diabetes is associated with alterations in the bone marrow, as shown by osteoblast apoptosis [101]. This finding may be relevant to a possible decreased recruitment of bone marrow-derived stem cells to the wound site.

Wound Bed Preparation: Critical Paradigm for Diabetic Foot Ulcers

Advances in the treatment of diabetic foot ulcers have relied heavily on concepts developed for acute wounds. In the last few years, however, a paradigm for addressing chronic wounds, including diabetic foot ulcers, has emerged and is widely recognized. We first discussed this concept in 2000. The WBP concept developed in the wake of regulatory approval of advanced wound healing products (i.e., topical PDGF and bioengineered skin) for chronic wounds. It was quickly realized that, strangely, the initial clinical results with these advanced and commercially available products did not match their greater preapproval efficacy. We realized that a better readiness of the wound bed was in order to allow advanced therapeutic agents to work, and we used the term "wound bed preparation" for this paradigm [1]. The main point, however, is that this approach represents a way to emphasize how, in multiple ways, the interventions intimately involved in healing chronic wounds are different than those required for acute wounds [11, 12]. With new insights and therapeutic modalities become available, for example stem cells (as described in the next sections), we may be talking more about "wound bed reconstitution." The critical concept is that, once appropriate steps have been taken to optimize the wound bed, then the normal endogenous process of wound healing is going to be facilitated [12]. It is important to note that WBP is more than surgical debridement alone, but rather a very comprehensive approach aimed at reducing edema and exudate, eliminating or reducing the bacterial burden and, importantly, correcting the abnormalities discussed earlier as contributing to impaired healing. There are both basic and more advanced approaches to wound bed preparation/optimization. Basic aspects, as with compromised acute wounds, include debridement, infection control, edema removal, and surgical correction of underlying defect. More advanced aspects, for which we certainly do not have all the answers yet, may include attempts at wound bed reconstitution, as with the use of stem cells and other biological agents. In turn, reconstitution of certain elements of the wound bed (for example, endothelial cells, proper extracellular matrix components) is very likely to improve the amount of exudate, edema, keratinocyte migration, etc. Therefore, it is difficult to separate the wound bed from the therapeutic agents being used. It is a two-way street and a highly synergistic process.

Therapeutic Advances Interacting with Wound Bed Preparation

As stated throughout this review, important and intimate links exist between debridement, WBP, and therapeutic advances. In the last few years, we have seen the development and marketing of very sophisticated products for impaired healing.

These products, whether they are growth factors or tissue engineering constructs, represent the culmination of decades of basic research. As we have already mentioned, the efficacy of many advanced therapeutic agents has not fully matched the expectations, partly because the standards of care for some chronic wounds, including diabetic foot ulcers, were not adequate. There are now a number of guidelines that have been published, including one from the Wound Healing Society [102–104]. As is often the case in medicine, and somewhat anti-intuitive, products and drugs actually may advance our understanding of pathophysiology and in turn lead to better overall clinical approaches. The same can be said about surgical procedures. For example, the process of surgical debridement of diabetic foot ulcers becomes more than simply removing necrotic tissue; at the same time, one is also removing the excessive bacterial burden and, possibly, the phenotypically abnormal cells that may be present in and around the wound (Fig. 13.2). Another example is the removal of edema, which is also critical in the management of diabetic ulcers. Edema removal decreases the chronic wound fluid that has been shown to be deleterious to resident cells and which may enhance bacterial colonization and trap growth factors [6]. Therefore, in the context of WBP existing therapies can be integrated better with pathophysiological principles [1, 11, 12]. An important consideration is that the relationship between WBP and advanced wound healing products is not a one-way street. We have found that even advanced therapies may be thought of as methods for improving WBP because ultimately such therapeutic agents are accelerating the endogenous process of wound healing.

Growth Factors

Over the last two decades, several recombinant growth factors have been tested for their ability to accelerate the healing of chronic wounds. Among others, some promising results have been obtained with the use of epidermal growth factor (EGF) for venous ulcers [105], fibroblast growth factor (FGF) [106], and PDGF for pressure ulcers [107]. However, at least in the USA, the only topically applied growth factor that is commercially approved for use is PDGF. In randomized controlled clinical studies, PDGF has been shown to accelerate the healing of neuropathic diabetic foot ulcers by approximately 15% [3, 4]. Recently, there has been controversy about an increasing risk of systemic malignancy developing with the use of PDGF (beclapermin) application to wounds. A recent publication suggests that beclapermin does not increase malignancy [108]. It is probably wise to use caution and advice patients properly until this important issue is completely resolved.

One may wonder why we do not have a greater number of growth factors approved for clinical use, and why the results of clinical trials have not been of greater magnitude, as we might have predicted from preclinical data. A number of explanations can be given for this. Inadequate peptide dosage and delivery, and possibly the need for combinations of growth factors are some of the problems hypothesized to explain the lack of more dramatic clinical effects. It is also possible, however, that closer attention should have been paid to appropriately preparing the chronic wound before treatment with the growth factor being tested in clinical trials. Notably, there is evidence that the aggressive approach to surgical debridement in the initial PDGF trial for diabetic neuropathic ulcers seems to have worked synergistically with the application of the growth factor [5]. It is important to note that the treatment of chronic wounds has been evolving in the last few years, and it might be argued that the increased number of randomized clinical trials for chronic wounds has improved standard wound care. We predict that in the future new products will need to perform much better than control to show efficacy.

Bioengineered Skin

Another major advanced treatment that can improve WBP is cell therapy, such as with the use of bioengineered skin [7, 8]. A number of bioengineered skin products or skin equivalents have become available for the treatment of acute and chronic wounds, as well as for burns. Since the

initial use of cultured keratinocyte sheets [109, 110], several more complex constructs have been developed and tested in human wounds. Skin equivalents may contain living cells, such as fibroblasts, keratinocytes, or both [111–115], while others are made of acellular materials or extracts of living cells. We have recently published an extensive review of the different types of constructs that are available [7]. Some allogeneic constructs consisting of living cells derived from neonatal foreskin have been shown to accelerate the healing of neuropathic diabetic foot ulcers in randomized controlled trials, and are available for clinical use [9, 10]. The clinical effect of these constructs is between 15 and 20% over conventional "control" therapy. One of the important arguments relates to what constitutes an appropriate control. In the US trials, saline-soaked gauze and off-loading have generally been accepted by the Food and Drug Administration as the control. However, the methods for off-loading differ in many countries, and the primary wound dressings to be used are also subject to controversy [24]. Truly prospective trials need to be done to determine the contribution of off-loading done with contact casting and how this approach can improve the outcome in patients treated with advanced biological products.

Bioengineered skin may work by delivering living cells, which are said to be "smart" in engineering terms, and thus capable of adapting to their environment. There is evidence that some of the living constructs are able to release growth factors and cytokines, but this cannot yet be interpreted as being their mechanism of action [116]. It should be noted that some of these allogeneic constructs do not survive for more than a few weeks when placed in a chronic wound [117, 118]. A particular aspect of tissue engineering we have been focusing on is whether a "priming" step of the construct, performed in vitro just prior to application to the wound, could augment the favorable biological effects of constructs in WBP and, ultimately wound closure. Indeed, our group has shown that priming for 24 h with increased concentrations of tissue culture media leads to a very highly significant, sometimes several hundred-fold, increase in certain cytokines and growth factors. It is our hypothesis that a priming step would jump-start or unfold the biological program of the construct before it is applied to the more hostile wound microenvironment, where it can be rapidly broken down [7]. Among the cytokines, we have found to be highly increased from the priming step are IL-6, IL-11, but many other overexpressed genes are also capable of attracting stem/progenitor cells to the wound (Falanga 2011, unpublished). In an ongoing pilot study in human wounds, we have evidence that the priming step of a living bilayered bioengineered skin construct results in epiboly of the construct evident in vivo by histological analysis. Although we have observed epiboly of that particular construct in vitro [119], this is the first time we have noted it in human wounds.

Gene Therapy and Stem/Progenitor Cells

Among the advanced but still investigational treatments for chronic wounds stand gene therapy and the use of stem cells. As we have discussed, a spectrum is likely to evolve over the next few years, going from WBP to wound bed reconstitution. Gene therapy and stem cells have the potential to drastically alter the wound bed and may thus be at the right end of the spectrum, toward wound bed reconstitution. For some time now, there has been ample technology for introducing certain genes into wounds by a variety of physical means or biological vectors, including viruses. There are ex vivo approaches, where cells may be manipulated before reintroduction into the wound, to more direct in vivo techniques, which may rely on simple injection or the use of the gene gun [120]. Inability to achieve stable and prolonged expression of a gene product, which has been a problem in the gene therapy treatment of systemic conditions, can actually be an advantage in the context of nonhealing wounds, where only transient expression may be required. Most of the work with gene therapy of wounds has been done in experimental animal models. However, there are promising indications that certain approaches may work in human

wounds. For example, the introduction of naked plasmid DNA encoding the gene for vascular endothelial growth factor (VEGF) has been reported to enhance healing and angiogenesis in selected patients with ulcers from arterial insufficiency [121]. Undoubtedly, the area of gene therapy for chronic human wounds could become more active in the next few years. The introduction of the gene, rather than its product, i.e., a growth factor, is seen as a less expensive and potentially more efficient delivery method. A pilot safety study of the PDGF gene delivered with a replication-incompetent adenoviral vector was recently reported [122].

An extension of the hypothesis that cell therapy may be required for reconstitution of the wound bed and to accelerate closure of chronic wounds is the notion that stem/progenitor cells might offer greater advantages than fully differentiated cells. Stem cells can differentiate into a variety of cell types, including fibroblasts, endothelial cells, and keratinocytes, which are critical cellular components that may require replacement in chronic wounds.

What sets stem cell therapy apart from other advanced therapies is that it could directly reconstitute the cellular components of the wound bed. Although recent developments with embryonic stem cell therapy and with induced pluripotent stem cell therapy have been exciting, these latter approaches are not likely to have clinical application for many years [123]. On the other hand, adult stem cell therapies have immediate clinical application. This is because clinicians can rely on the more than 40-year experience of a related field, bone marrow stem cell transplantation, to design stem cell therapies. In fact, the most commonly studied form of stem cell therapy employs bone marrow-derived cells. Specifically, bone marrow is aspirated, separated, and cultured, and a specific subset of stem cells, for example mesenchymal stem cells (MSCs), is selected for and amplified in vitro before application to wounds [124, 125]. After showing preliminary proof of principle that bone marrow-derived stem cells could lead to the healing of chronic wounds [126], we established reliable culture conditions and used a fibrin spray system to apply autologous bone marrow-derived MSCs to both chronic and acute wounds; accelerated wound healing took place [125]. Importantly, our study showed that healing did not take place unless we applied at least 1 million stem cell per cm^2 of wound surface. Another study of three cases of chronic leg wounds treated with bone marrow-derived cells also showed improvement [127]. Then, in a trial involving 20 patients with chronic wounds, cultured bone marrow-derived cells placed in an artificial collagen dermis and applied to chronic wounds improved the wounds in 18 patients [128].

Stem cell therapy studies of diabetic foot wounds have also had promising results. Two case reports of the successful treatment of diabetic foot wounds treated with MSC therapy have been reported [129, 130]. In addition, a randomized controlled study of bone marrow-derived stem cells compared to standard dressings, specifically for diabetic foot ulcers and Buerger's disease, found that in the diabetic foot ulcer group the ulcer size decreased significantly as compared to the control group at 12 weeks [131]. The results of MSCs therapy on wound healing have been dramatic in some instances, moderate in others, but there has been no large randomized controlled study.

A different approach to stem cell therapy for wound healing, and which circumvents the need for bone marrow aspiration, also derives its methodology from bone marrow transplantation. In current bone marrow transplantation, the cytokine granulocyte colony stimulating factor (GCSF) is used to mobilize stem cells out of the bone marrow and into the peripheral blood, where the stem cells can then be harvested by apheresis. However, rather than been harvested, the stem/progenitor cells may be allowed to circulate and theoretically home to the wound site. Most of the GCSF stem cell studies have been performed on healing of injury to the myocardium [132] or to the spinal cord [133]. In a study of cutaneous wound healing following GCSF treatment, mouse studies suggested some improvement in wound healing, as did one human subject with a chronic wound [134]. Moreover, a meta-analysis of five randomized trials of systemic GCSF administration in patients with diabetic foot infections and/or

infected ulcers showed that the most significant effect was the reduction in the need for surgical interventions, including amputations [135, 136]. A related approach to stem cell therapy could be the fractionation of stem cell subtypes after GCSF mobilization that can then be harvested and placed directly on wounds. Studies using these approaches are ongoing. However, to improve the clinical efficacy of stem cell therapy, we will need to understand the precise mechanism by which stem cells can reach and exert their effects on the wound site.

Unfortunately, the steps in the mechanism of how adult stem cell therapy might work are still unclear. In studies using MSCs, there is evidence to suggest that these stromal stem cells may differentiate to replace missing tissue in the wound bed [125]. However, the evidence is suggestive but not conclusive; it is experimentally difficult in human subjects to label and track MSCs as they differentiate in vivo within wounds. Stem cell therapies involving GCSF may involve slightly different mechanisms. GCSF mobilizes predominantly hematopoietic stem cells (HSCs). On the one hand, some argue that HSCs may transdifferentiate to some extent to replace tissue missing in a defective wound bed [137, 138]. Other experts contend that, rather than by transdifferentiation, the GCSF-mobilized HSCs mainly exert paracrine effects on endogenous stem cells within the wound bed [139, 140]. It is possible that GCSF may mobilize MSCs [141] and/or that the newly discovered very small embryonic-like stem cells (VSELs), which have many of the markers and properties of embryonic stem cells [142]. In summary, the precise mechanisms of stem cell therapy have yet to be elucidated. If we were to understand the precise ways in which stem cells can regenerate tissue, these ways could be optimized to produce clinically significant improvements in WBP.

Summary

A rational strategy for addressing diabetic foot ulcers will likely require greater understanding of the clinical factors involved as well as the pathophysiological components that underlie their impaired healing. Greater therapeutic aggressiveness is required as well. For example, existing advanced therapeutic products tested in diabetic foot ulcers, such as growth factors and skin equivalents, have focused entirely on neuropathic ulcers of the metatarsal heads; arterial insufficiency and the more complex heel ulcers have been exclusion criteria in those trials. Such purely neuropathic ulcers are easier to treat, and many clinicians believe that those ulcers can be effectively treated with sound surgical debridement and off-loading. While it may be argued that accelerating the healing of noncomplicated neuropathic foot ulcers may prevent infection and even amputation, more needs to be done to show cost-effectiveness to our society as a whole. Still, considerable progress has been made, and a number of therapeutic approaches, including improved standard care, are now available. It is hoped that continued advances will come about which, when combined with basic medical and surgical approaches, will accelerate healing of chronic wounds to an extent that is still not possible with present therapeutic agents. WBP has changed and continues to alter the approach to diabetic foot ulcers and other types of chronic wounds. Debridement is seen as more than the removal of unwanted necrotic tissue and callus. As illustrated in Fig. 13.1, surgical debridement may be a way to also decrease the bacterial burden and to remove phenotypically altered cells that may be interfering with the healing process. As stated earlier, debridement in diabetic foot ulcers is preferably done by surgical means, although there is a need for better topical debriding agents. Presently, there is also reliance on slow release antiseptics (silver or iodine based) and, to a lesser extent, on autolytic debridement with occlusive dressings (Fig. 13.1). The emphasis by regulatory agencies to determine the efficacy of debriding agents in terms of healing endpoints has not helped; industry has been reluctant to embark on such expensive studies, and patients may be suffering from this regulatory link between debridement and healing outcome. Hopefully, this regulatory policy will change in the future. What has also become clear is that

therapeutic agents may actually work by improving WBP, thus allowing the endogenous process of wound healing to move forward. As a result of many advances, including the concepts of maintenance debridement and WBP, the standards of care for diabetic foot ulcers have improved. As stated earlier, because the control group will receive better care in therapeutic trials, it will become more difficult to prove the effectiveness of novel therapeutic agents. However, we should strive for a "quantum" jump in the way we deal with diabetic foot ulcers and other chronic wounds. Perhaps, the use of gene therapy, stem/progenitor cells, may provide a quantum advance in accelerating diabetic foot ulcer healing. With acceptance of the concept of WBP, of which debridement is an integral part, we will move toward wound bed reconstitution, which will require more active and innovative therapeutic approaches.

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Foot Pressure Abnormalities in the Diabetic Foot

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Abstract

For decades, foot pressure measurements have been used to evaluate many medical conditions. Early techniques to assess plantar foot pressure were simple, yet innovative, methods that provided investigators with semi-quantitative data. The introduction of the optical pedobarograph significantly improved the accuracy of foot pressure measurements. Measurement of foot pressures has advanced over the years and now includes computer technology that allows for accurate and reproducible measurements.

Foot pressure measurements and plantar ulceration have been extensively researched in the insensate foot (Wagner Orthopedics 10:163–72, 1987; Pollard et al. J Biomed Eng 5:37–41, 1983; Lang-Stevenson et al. J Bone Joint Surg 67B:438–42, 1985; Boulton et al. Diabetes Care 7:73–7, 1987; Boulton et al. Diabetes Care 6:26–33, 1983; Betts and Duckworth J Bone Joint Surg 67:79–85, 1985; Boulton et al. Etiopathogenesis and management of abnormal foot pressures. In: Levin et al. editors. The diabetic foot, 5th ed. St. Louis: Mosby; 1993. p. 233–46; Fernando et al. Diabetes Care 14:8–11, 1991; Veves Foot 2:89–92, 1991; Young et al. Diabet Med 5:55–7, 1992; Cavanagh et al. Diabetes Care 14:750–5, 1991;

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Donaghue and Veves Orthop Phys Ther Clin N Am 6:1–16, 1997; Rich and Veves Wounds 12(4):82–7, 2000; Sarnow et al. Diabetes Care 17:1002–6, 1994; Veves et al. Diabetologia 35:660–3, 1992; Veves et al. Diabet Med 12:585–9, 1995; Ctercteko et al. Br J Surg 68:608–14, 1981; Stokes et al. Acta Orthop Scand 46:839–47, 1975; Brand Insensitive feet, a practical handbook of foot problems in leprosy. The Leprosy Mission: London; 1984). In western societies, the principal cause of the insensate foot is diabetes mellitus though in other regions of the world, leprosy remains an important contributing factor (Brand Insensitive feet, a practical handbook of foot problems in leprosy. The Leprosy Mission: London; 1984). In fact, the study and work of patients with Hansen's disease have allowed for an understanding of the pathophysiology of the insensate foot and its principles of treatment (Brand Insensitive feet, a practical handbook of foot problems in leprosy. The Leprosy Mission: London; 1984). Off-loading plantar pressure ulcerations is a fundamental key in the treatment of these lesions and yet it is a feature that is often underappreciated and therefore underutilized. Even in this day and age, off-loading a plantar ulceration with a dressing, padding, or even a total contact cast is considered bourgeois and even proletarian by some who care for these wounds using only debridement instruments and dressings. An understanding of foot pressures, shear, and motion about a plantar foot ulceration should be a prerequisite for one practicing in this area. Moreover, the measurement of foot pressures can be clinically valuable in other settings, such as in the evaluation and treatment of the foot in patients with inflammatory arthritic deformities, posttraumatic foot deformities, congenital foot deformities, acquired foot deformities such as hallux valgus, and postsurgical changes as well as dynamic foot evaluation in the setting of sports medicine.

Keywords

Foot pressures • Electrodynagram • Novel systems • F scan system • Natural history of foot pressure • Abnormalities in diabetes mellitus • Foot ulceration • Off-loading the diabetic foot • Footwear • Hosiery • Shoewear • Insoles • Orthotics

Introduction

For decades, foot pressure measurements have been used to evaluate many medical conditions. Early techniques to assess plantar foot pressure were simple, yet innovative, methods that provided investigators with semiquantitative data. The introduction of the optical pedobarograph significantly improved the accuracy of foot pressure measurements. Measurement of foot pressures has advanced over the years and now includes computer technology that allows for accurate and reproducible measurements.

Foot pressure measurements and plantar ulceration have been extensively researched in the insensate foot [1–19]. In western societies, the principal cause of the insensate foot is diabetes mellitus though in other regions of the world, leprosy remains an important contributing factor [19]. In fact, the study and work of patients with Hansen's disease has allowed for an understanding of the pathophysiology of the insensate foot and its principles of treatment [19]. Off-loading

plantar pressure ulcerations is a fundamental key in the treatment of these lesions and yet it is a feature that is often underappreciated and therefore underutilized. Even in this day and age, offloading a plantar ulceration with a dressing, padding, or even a total contact cast is considered bourgeois and even proletarian by some who care for these wounds using only debridement instruments and dressings. An understanding of foot pressures, shear, and motion about a plantar foot ulceration should be a prerequisite for one practicing in this area. Moreover, the measurement of foot pressures can be clinically valuable in other settings, such as in the evaluation and treatment of the foot in patients with inflammatory arthritic deformities, posttraumatic foot deformities, congenital foot deformities, acquired foot deformities such as hallux valgus, and postsurgical changes as well as dynamic foot evaluation in the setting of sports medicine.

Methods of Measuring Foot Pressures

Out-of-Shoe Methods

One of the earliest studies to assess pressure on the plantar aspect of the foot was that of Beely in 1882 [20]. Subjects ambulated over a cloth-filled sack filled with plaster of Paris to produce a footprint. Beely postulated that the plaster would capture the plantar aspect of the foot with the highest load, representing the deepest impression. However, this primitive technique was limited because it represented a crude measurement of the total force of the foot creating the impression rather than the dynamic pressures underneath the foot during gait. Moreover, this method was strictly qualitative and therefore susceptible to both inter- and intraobserver unreliability.

In 1930, Morton [21] described a ridged, deformable rubber pad, termed the *kinetograph.* This pad made contact with an inked paper placed underneath the foot while the subject ambulated over the pad. The kinetograph examined the relationship between the static and rigid foot deformity and was the first documented attempt to measure foot pressures rather than forces. Elftman [22] further developed a system that allowed for the observation of dynamic changes in pressure distribution as the subject ambulated. This device was called the *barograph.* It consisted of a rubber mat that was smooth on top yet studded with pyramidal projections on the bottom. The mat was placed on a glass plate, and as subjects ambulated over the mat, the area of contact of the projections increased according to changes in the pressures under the foot. A video camera recorded the deformation pattern of the mat from below as the subject walked on the mat.

Similarly, in 1947, Harris and Beath [23] used a similar method to study foot problems and related foot pressure changes in a large group of Canadian soldiers. Their device, called the *Harris–Beath Mat*, used a multilayered inked rubber mat that allowed contact with a piece of paper below. When pressure was applied to the mat with ambulation, the ink escaped from it, thereby staining the paper. Thus, the density of the inked impression was dependent on the applied pressure. By using this technique, Barrett and Mooney [24] found high loading under the feet of diabetic subjects. The major problem with this device, however, was that it could not be calibrated to various degrees of foot pressures and therefore the Harris–Beath mat would saturate at levels within the normal limits of foot pressures. Furthermore, the amount of ink placed onto the mat could not be standardized. Silvino and associates [25], however, calibrated the Harris–Beath mat by using a contact area of known size and weight, thereby producing both qualitative and semiquantitative data.

A similar device to the Harris–Beath mat is the *Podotrack System* (Medical Gait Technology, the Netherlands). The system is based on the principles of the Harris–Beath mat. However, the footprint impression is produced by a chemical reaction with carbon paper instead of ink. The Podotrack system has a few advantages over the Harris–Beath mat. For example, there is a standard ink layer that is carbon paper. Furthermore, the system can be calibrated with a scale representing shades of colors corresponding to foot pressures. In 1994, a study

reported that the Podotrack system provided reproducible results in 61% of the foot pressure values when compared with those obtained from the pedobarograph [26]. Furthermore, the Podotrack and pedobarograph systems were comparatively examined. By placing the Podotrack system on top of the pedobarograph, one could obtain real-time data as subjects ambulated over both systems.

In 1974, Arcan and Brull [27] described a system that had the capability of providing more detailed, though semiquantitative, information regarding foot pressure distribution. The apparatus consisted of a rigid transparent platform with optical filters. An optically sensitive elastic material and reflective layer were combined together. Foot pressure measurements were performed either statically or dynamically, and the changes in motion of the foot were recorded using a video camera.

An earlier quantitative technique to measure foot pressures was described by Hutton and Drabble in 1972 [28]. Their device consisted of a force plate in which 12 beams were suspended from 2 load cells. These load cells were attached to several sets of wire strain gauges that permitted the measurement of longitudinal tension. The apparatus was placed onto the walkway because subjects could step on and off the plate during their gait cycle. By using this technique, Stott and colleagues [29] scrutinized the load distribution in subjects with and without pes planus (flatfeet) and hallux valgus deformities. The distribution of peak loads was expressed as a percentage of body weight and the results demonstrated that the load of the control subjects was low in the midfoot and high in the forefoot. However, there was considerable variation in loads across the ball of the foot. Conversely, in subjects with pes planus, an increased load was appreciated. In addition, their study reported that subjects who had greater body weight tended to have higher peak loads on the lateral aspect of the foot.

In a later study by Stokes and associates [18], foot pressures, body weight, and foot ulceration in diabetic patients were examined. Their study was remarkable in that it demonstrated that foot ulcers occurred at sites of maximal load. Furthermore, increased loads in patients with foot ulceration were related to their body weight when they were compared to healthy controls and diabetic patients without ulcerations.

Subsequently, Ctercteko and colleagues [17] developed a computer system that measured vertical foot pressures of the sole on the foot in diabetic patients with and without ulceration and in control subjects during ambulation. The system consisted of a load-sensitive device divided into 128 strain gauge load cells with a 15 × 15-mm surface area that was built into an 8-m walkway. The foot was divided into eight areas, and the output from each load cell was processed and transmitted into a microcomputer. An evaluation of the data provided quantitative values for the sites of peak force and pressure under the foot and duration of contact time. It demonstrated that in both groups of diabetic subjects, with and without ulceration, a similar pattern of reduced toe loading was noted when compared with control subjects. This resulted in a higher loading at the metatarsophalangeal head region, where the majority of ulcerations were present. These results confirmed that foot ulceration occurred at sites of maximal load under the foot.

The *optical pedobarograph* is a device that measures dynamic plantar pressures. The device is based on an earlier system described by Chodera in 1957. The optical pedobarograph consists of an elevated walkway with a glass plate that is illuminated along the edge and covered with a thin sheet of soft plastic [30]. The light is then reflected internally within the plate when no pressure is applied. However, when a subject stands or ambulates across the surface, light escapes from the glass at these pressure points and is scattered by the plastic sheet, producing an image of the foot that can be seen below. A monochromatic camera detects the image, and the pressure at any given point can be determined automatically by measuring the intensity of that image at that specific point. This system has high spatial resolution and, thereby, allows an accurate measurement of high foot pressures under small areas of the foot with satisfactory precision. The optical barograph is used

widely in the examination of high foot pressures, such as in the diabetic foot. Additionally, this system has been used for interventional trials that study the effectiveness of off-loading high-pressure areas. However, this system is limited to measurements of barefoot pressures and, therefore, does not allow the evaluation of in-shoe pressures. Moreover, this system requires substantial space and is not easily portable.

In-Shoe Methods

Developments in computer technology have enabled microprocessor-like recording devices to measure in-shoe foot pressures. In 1963, Bauman and Brand [31] recognized the limitations of barefoot pressure measurements in the insensate and deformed foot. The apparatus they devised was composed of thin pressure-sensitive transducers that were attached to suspected areas of high pressure underneath the foot. Although this method was expensive and elaborate in design, it proved that in-shoe foot pressures were both feasible and indeed useful. In essence, Bauman and Brand laid the foundation for the design of less expensive devices to become available for general use.

Electrodynogram

The aforementioned principles were used in the mid-1970s to develop the electrodynogram system (EDG System, Langer Biomechanics Group, Deer Park, New York). It has been used in both clinical and research settings [32, 33]. This apparatus is a computer-assisted system that uses seven small, separate sensors that adhere to the plantar aspect of the foot. They are attached by cable and relay information into a computer pack carried by the subject. In-shoe and out-of-shoe walking pressures can be evaluated. However, the system is limited because only peak pressures can be measured where the sensors are placed. Hence, this system cannot provide pressure information pertaining to the entire plantar aspect of the foot.

Novel Systems

Novel has pressure-measuring systems for computer-assisted and image-generating devices to record both in-shoe and out-of-shoe dynamic foot pressures. Its design permits the examination of the entire plantar aspect of the foot. The systems measure a change in capacitance in two wires separated by an insulating layer when a change in the distance between the two wires occurs. The direct measurement is change in electrical resistance. Pressure is then indirectly measured. The EMED platform system is mat based on the principle that a change in the pressure on a wire causes a similar change on its electrical capacitance, thereby allowing foot pressures to be measured by recording electrical flow through the mat. Another Novel system that has evolved over the years is the Pedar®-X system incorporating sensors in very thin insoles (1.9 mm) that measure pressures on the entire plantar aspect of the foot. The data is transferred via straight connection to a personal computer, via wireless, or stored in flash memory to be downloaded later. Measurements are obtained with satisfactory reliability. Gait analysis can be compromised if connecting cables or thick insoles alter a subject's gait pattern. Therefore, the use of thin insoles and wireless connection enhances the integrity of data collection from subjects by minimizing gait alteration. The system has been used in a variety of clinical applications, including the evaluation of plantar pressure distribution in young adults with ankle fractures and diabetic patients with foot ulcerations or Charcot neuroarthropathy, as well as some sports medicine applications [34].

F Scan System

At the author's unit, much study has been conducted using the FSCAN System. This system is a high-resolution, computerized pressure, force, and gait analysis program that was designed according to the principles described previously [35, 36]. The hardware system collects both static and dynamic plantar pressures, force, and contact

area data by using either mats (MatScan or HR Mat™) or (F-scan) in-shoe sensors. The mat sensors measure foot pressures, force, and contact area as the subject freely ambulates or stands over the mat without electronic cables that may potentially influence an individual's foot function, gait pattern, or standing position (Fig. 14.1a, b).

The F Scan system uses in-shoe sensors that are ultrathin (0.007 in./0.15 mm) and flexible, and that conform to the interface between the plantar foot and the inner sole of the footwear. Each sensor consists of 960 sensing locations referred to as sensing cells or sensels that are distributed uniformly across the entire plantar aspect of the foot [36, 37]. These sensing elements provide the spatial resolution required for detecting differential pressures exerted over relatively small areas. The unique F-Scan sensor can be trimmed to sizes and inserted into the subject's footwear. The sensor does not interfere with the subject's foot function and gait or reduce the true pressures by accommodating to the existing deformities (Fig. 14.1c).

The sensor plugs into a 3.7-oz analog-to-digital converter cuff unit about the ankle. This is attached to one or both of the subject's legs. A cable connects the cuff unit to a hub which in turn is connected to the computer via a USB connection for the F-Scan tethered system or to the wireless (transmitter)/datalogger (receiver) unit around the waist of the subject. The latter is called the F-scan Wireless/Datalogger and is nontethered. For clinical use, the calibration method entails applying a known load, which is commonly the subject's weight, over the sensing cells. By using the prescribed calibration method, an accuracy method of ±7.3% may be obtained.

For research use, the scanner system may use an additional operational technique (via the use of an air bladder) called *equilibration.* Equilibration assigns scaling factors to each sensing cell. It is used to increase the uniformity of sensing cells within a given sensor. Therefore, this dampens the effect of cell-to-cell variation without reducing the spatial resolution. If this additional equilibration procedure is followed, the accuracy of the pressure measurement system is within 3–5%. The F-Scan in-shoe system has the capability and option to be upgraded to include a sensor mat that can measure out-of-shoe foot pressures. Likewise, the MatScan and HR Mat

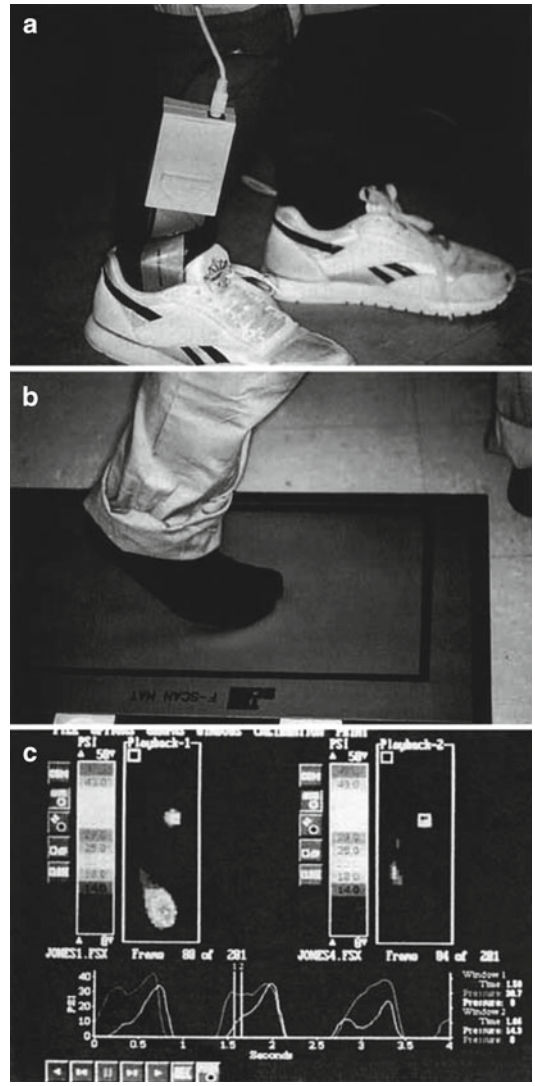

Fig. 14.1 (**a**) A subject walking with the FSCAN sensor inserted in his shoes. Changes in the electrical capacitance, which are related to the applied pressures on the sensors during walking, are transmitted via the cable to an IBM-compatible computer, where they are analyzed using the FSCAN software (ref. 12). (**b**) The FSCAN mat, which is based on the same principles used to design the FSCAN sensors, can be used to measure pressures of bare feet. The mat is compatible and is connected to the same apparatus used for in-shoe measurements (ref. 12). (**c**) Computer-assisted analysis of a foot step. The highest foot pressures in this subject are seen underneath the heel and the first metatarsal area (ref. 12)

floor mat systems also have the capability and option to be upgraded to include the in-shoe sensor that can measure inside footwear. These systems are advantageous because of their simplicity, easy storage, and reproducibility of data. Satisfactory reproducibility has been reported in the great majority of studies that have used this system [37, 38].

The sensors, however, have potential limitations. For example, the MatScan sensor has decreased resolution compared with the F-Scan in-shoe and HR MAT floor mat sensors. Furthermore, because the in-shoe sensor is very thin, it may fail from wrinkling and breakage and thereby yield incorrect data [35]. Rose and colleagues [35] found that two insole sensors gave different results when used on the same subject. Additionally, there was a decline in sensitivity if the sensor was used 12 times. However, the newer Sport Sensors are less susceptible to wrinkling, breakage, and decline in sensitivity. Altering the shoe insole can also affect foot pressure measurement. However, this is not a limitation but an advantage. Material type, shape, and density affect contact area, load absorption, and force vector orientation, which in return alter force patterns, pressure profiles, and peak values. The high resolution of the F-Scan in-shoe sensor, therefore, allows one to measure the effect of shoe insole alterations useful in clinical and research applications. Likewise, the high resolution of the HR Mat floor mat sensor (like the F-Scan in-shoe sensor) supports visualization and pressure, force, and contact area measures of small feet such as that of children and other small components and anatomical landmarks of the plantar foot.

Natural History of Foot Pressure Abnormalities in Diabetes Mellitus

Foot pressure measurements in diabetic patients have been attempted for over 30 years. Stokes et al. [18] used a segmental force platform to study 37 feet of 22 diabetic patients. High loads were found at the sites of ulcers. Patients with high loads under the feet were also heavier in weight than those with lower loads. Toe loads in patients with ulcers were found to be reduced. A shift of maximum loads to the lateral foot in neuropathic patients was also reported. In a subsequent study, Ctercteko and colleagues [17] confirmed all these findings, except for the lateral shift of maximum loads. Conversely, a medial shift was discovered in their study. In another study, neither a medial nor a lateral shift was found. However, peak pressures under the heel occurred with a lower frequency in all diabetic patients compared with patients without diabetes [9]. This finding may suggest an early change when foot pressures start rising under the forefoot but still remain within normal limits, as in patients without neuropathy.

In previous studies, we have shown that in diabetic neuropathic patients there is a transfer of high pressures from the heel and the toes to the metatarsal head [9]. The main reasons for this transfer are neuropathy and limited joint mobility [8, 9]. Neuropathy leads to atrophy of the intrinsic musculature of the foot and clawing of the toes which may result in prominent metatarsal heads under which high pressures occur. Though we realize that forefoot pressures are increased in the feet of patients with diabetic neuropathy, it has also been demonstrated that rearfoot pressures also increase as well, especially in moderate to severe neuropathy [39]. Moreover, a transfer of peak pressures from the rearfoot to the metatarsal heads was noted in patients with diabetic neuropathy [13]. Accordingly, it has been demonstrated that the ratio of forefoot to rearfoot pressures is indeed increased in severe diabetic neuropathy [39]. This further indicates the inability of the neuropathic foot to distribute foot pressure and avoid the development of high foot pressures. Additionally, limited joint mobility impairs the ability of the foot to absorb and redistribute the forces related to impact on the ground while walking. Its effects on the foot appear to be global in nature and include reduced motion at the ankle, subtalar, and first MTP joints [40]. Vital musculoskeletal structures, such as the Achilles tendon and plantar fascia, may also be involved with changes, such as shortening and thickening of both structures [41]. The foot

becomes stiff, rigid, and less able to dampen pressure. Consequently, this contributes to the development of high foot pressures and subsequent ulceration [9, 14]. Additionally, patients with diabetes mellitus may also have reduced plantar soft tissue thickness [42, 43], which further reduces the ability of the foot to mitigate foot pressures. An inverse relationship exists between reduced plantar tissue thickness and elevated foot pressures in some patients with diabetes mellitus [44].

Foot Pressures and Foot Ulceration

Foot ulceration is a significant cause of morbidity in patients with diabetes mellitus and can lead to prolonged lengths of hospital stay. Numerous risk factors for foot ulceration in diabetes have been confirmed. While these include limited joint mobility, peripheral neuropathy, and vascular disease, high plantar pressures have been implicated as significant predisposing factors leading to ulceration in population-based and clinical studies seeking to quantify such relationships.

Boulton and associates [5] were the first group to employ the optical pedobarograph for research purposes to examine the relationship between high foot pressures and ulceration. In their study, diabetic patients with and without neuropathy and individuals without diabetes were examined to evaluate the relationships among foot pressures, neuropathy, and foot ulceration. Their results demonstrated that a significantly larger number of patients with diabetic neuropathy had abnormally high foot pressures compared with controls. Furthermore, patients with a previous history of foot ulceration had high pressures at ulceration sites. Because ulceration occurred at sites of high plantar foot pressures, foot pressure reduction, therefore, should lead to a reduced incidence of foot ulceration in neuropathic diabetic patients.

In a subsequent study performed by the same group, sorbothane shoe inserts were employed in an attempt to evaluate pressure reduction in diabetic patients [45]. Abnormally high foot pressures were measured in 33% of feet without insoles and in 6% of feet when using the insoles, thereby indicating that special accommodative insoles may help reduce plantar foot pressures in diabetic neuropathic patients.

In a prospective study that lasted 3 years and included diabetic patients with long-standing diabetes and neuropathy, Kelly and Coventry [46] also examined the long-term changes in plantar foot pressure. Their results demonstrated that important alterations of foot pressure distribution had occurred in a significant number of these subjects, some of whom had developed recurrent ulcerations at these sites of high pressure. Moreover, it was again confirmed that patients with neuropathy and the characteristic intrinsic-minus foot had abnormally high foot pressures measured at the metatarsal heads [15].

Definite proof that abnormally high pressures in diabetic patients were related to the development of plantar foot ulceration can be derived from a pivotal prospective study that followed a large number of patients for a mean period of 30 months [15]. During this study, plantar ulcers developed in 17% of all feet and 45% of feet with diabetic neuropathy. All of these ulcerations occurred in patients with high foot pressures at baseline, thereby suggesting that high foot pressures, especially in neuropathic patients, are predictive for the development of foot ulceration and may be useful for identifying at-risk patients (Fig. 14.2).

Given the correlation between foot pressures and foot ulceration, a study to evaluate the role between joint mobility and racial affinity in the development of high foot pressures was performed. This study demonstrated that black subjects without diabetes and patients with diabetes have increased joint mobility compared to Caucasian healthy subjects and patients with diabetes [16]. A higher degree of joint mobility would appear to correlate with lower peak plantar pressures and, therefore, a lower risk of foot ulceration.

Similarly, the role of neuropathy and high foot pressures in diabetic foot ulceration was evaluated [47]. In a cross-sectional multicenter study, the magnitude of association of several different risk factors for foot ulceration in patients with diabetes mellitus was determined. A cross-sectional

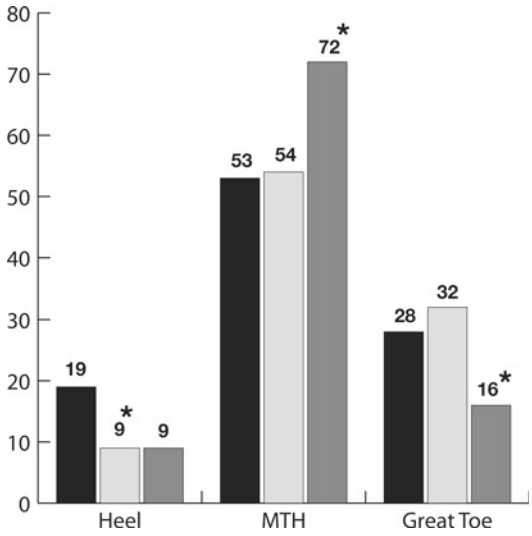

Fig. 14.2 Histogram demonstrating the distribution of peak pressures under the foot of healthy subjects (*black columns*), diabetic non-neuropathic patients (*gray columns*), and neuropathic diabetic patients (*white columns*). Peak pressures were more often under the metatarsal heads of the neuropathic patients while they were less often under the heel and great toe. It is also of interest that peak pressures under the heel were less frequent in the non-neuropathic patients (*: $p<0.05$) (ref. 15)

group of 251 subjects consisting of Caucasian, Black, and Hispanic races were studied. There was equal distribution of men and women across the entire study population. All patients underwent a complete medical history and lower extremity evaluation for neuropathy and foot pressures. Neuropathic factors were dichotomized (0/1) into two high-risk variables: a high vibration perception threshold (hiVPT) >25 V and inability to feel a 5.07 or smaller Semmes-Weinstein monofilament (Hi SWF). The mean dynamic foot pressures of three footsteps were measured using the FSCAN mat system with patients walking in stockings but without shoewear. Maximum plantar pressures were dichotomized into a high-pressure variable (Pmax6) indicating those subjects with pressures ≥6 kg/sq cm ($n=96$). The total of 99 patients had a current or prior history of ulceration at baseline.

The sensor was used in a floor mat system designed to measure barefoot or stocking-foot dynamic pressures. Maximum peak pressures for the entire foot were obtained without regard for specific location by averaging those obtained for three midgait foot steps and were then dichotomized into a high-pressure variable indicating those subjects with pressures ≥6 kg/sq cm.

With a specific focus on plantar foot pressures, joint mobility, and neuropathic parameters consistent with ulceration, this study demonstrated that patients with foot pressures ≥6 kg/sq cm were twice as likely to have ulcerations than those without high pressures, even after adjustment for age, gender, diabetes duration, and racial affinity. In the Black and Hispanic groups, significantly lower plantar pressures were demonstrated compared with the Caucasian group. High plantar pressures were relatively infrequent in the Black and Hispanic groups and were not found to be significant predictors of ulceration. Foot pressures ≥6 kg/sq cm were independently associated with ulceration, but to a lesser extent than the neuropathy variables (Tables 14.1 and 14.2).

This study demonstrated that the association of high foot pressures, hiVPT, and insensitivity to a 5.07 monofilament contributed to the development of foot ulceration. Furthermore, their group demonstrated significant racial difference in joint mobility, associated foot pressures, and the prevalence of ulceration among Caucasian, Black, and Hispanic patients. These findings have guided efforts at detecting diabetic patients at risk of ulceration by incorporating such parameters into screening programs. Foot pressures should be evaluated to detect those neuropathic individuals at risk of ulceration from excessive callus formation or repetitive stress [9, 10]. Although the two measures of neuropathy have the greater magnitude of effect, foot pressures should still be evaluated to detect those neuropathic individuals at risk of ulceration from excessive plantar callus formation or repetitive stress.

The Role of Foot Pressures as a Screening Method to Identify At-Risk Patients

Because diabetic foot ulceration is a preventable long-term complication of diabetes mellitus, screening techniques to identify the at-risk patient

Table 14.1 Logistic regression results for risk of ulceration

	Odds ratio (O.R.)	95% Confidence interval	*p*-Value
Univariate results			
Age[a]	1.02	1.00–1.03	0.019
Sex[b]	0.26	0.18–0.38	0.000
BMI	0.97	0.94–0.99	0.048
Diabetes duration[a]	1.04	1.02–1.06	0.000
Pulses	0.31	0.18–0.52	0.000
Pmax6	3.9	2.6–5.7	0.000
HiVPT	11.7	7.4–18.4	0.000
HiSWF	9.6	5.02–18.5	0.000
HiRisk	7.4	4.8–11.6	0.000
Multivariate results	(Controlling for age, sex, duration, race)		
Pmax6	2.1	1.32–3.39	0.002
HiVPT	4.4	2.58–7.54	0.000
HiSWF	4.1	1.89–8.87	0.000
HiRisk[c]	4.1	2.48–6.63	0.000

[a] O.R. per year of increase
[b] Reduced risk of ulceration in females relative to males
[c] Multivariate O.R. for interaction term without other neuropathic or pressure variables in model

Table 14.2 Multivariate logistic regression for ulceration by race, controlling for age, sex, and diabetes duration

	Odds ratio (O.R.)	95% Confidence interval	*p*-Value
Caucasian			
Pmax6	7.7	2.07–28.4	0.002
HiVPT	7.4	2.4–22.9	0.001
HiSWF	3.7	1.3–10.3	0.013
Black			
Pmax6	0.53	0.05–5.8	0.608
HiVPT	7.2	1.2–43.7	0.032
HiSWF	19.8	1.1–344.2	0.041
Hispanic			
Pmax6	2.1	0.38–11.5	0.395
HiVPT	6.6	2.3–18.5	0.000
HiSWF[a]	–	–	–

[a] Dropped due to perfect prediction of outcome

are probably the most important steps in reducing the rate of foot ulceration and lower limb amputation. To this end, various screening techniques have been proposed and are currently in use. These include the evaluation of vibration perception threshold (VPT), foot pressure measurements, joint mobility, and SWF 5.07 testing. Furthermore, a history of previous foot ulceration, Tc PO_2 level of <30 mmHg, and the existence of foot deformities have been shown to be risk factors for the development of diabetic foot ulceration. In our unit, a study evaluated plantar pressures and screening techniques to identify people at high risk for diabetic foot ulceration [48]. The objective of this study was to compare the specificity, sensitivity, and prospective predictive value of the most commonly used screening techniques for the identification of high risk

for foot ulceration in a prospective multicenter fashion. Furthermore, this study aimed to identify as many risk factors as possible and to develop a screening strategy that, by combining the detection of two or more risk factors, would provide the best tool for identifying the at-risk patient.

Two hundred and forty-eight patients from three large diabetic foot centers, including our own unit, were evaluated in a prospective study. Neuropathy symptom score (NSS), neuropathy disability score (NDS), VPT, SWF, joint mobility, peak plantar pressures, and vascular status were evaluated in each of the subjects. Patients were followed up every 6 months for a mean period of 30 months, and all new foot ulcers were recorded. The sensitivity, specificity, and positive predictive value of each risk factor were evaluated.

Foot ulcers developed in 73 patients during the study. Patients who developed foot ulcers were frequently men, had diabetes for a longer duration, and had an inability to detect a 5.07 monofilament. NDS alone had the best sensitivity, whereas the combination of the NDS and the inability to detect a 5.07 monofilament reached a sensitivity of 99%. However, foot pressures had the best specificity, and the best combination was that of NDS and foot pressures.

This study prospectively evaluated the association of several risk factors for foot ulceration. The results demonstrated that a high NDS obtained during a simple stratified clinical examination provided the best sensitivity in identifying patients at risk for foot ulceration, whereas high VPT, the inability to feel an SWF 5.07, and high foot pressures were independent factors. Furthermore, the combination of NDS and an SWF 5.07 (10 g) could identify all but 1 of 95 ulcerated feet. The use of these two simple methods in clinical practice can assist in identifying the at-risk patient, which is the first step in the prevention of foot ulceration. Foot pressures are often elevated in patients with diabetic neuropathy. However, as an initial tool by itself, the measurement of foot pressures is not very helpful in predicting the development of foot ulceration. This was demonstrated in this study and confirmed in a subsequent study [49]. In terms of predicting ulceration, foot pressure measurements are only useful when combined with other modalities, making them not very practical as an initial tool. They may be used as a valuable postscreening test in conjunction with assessing the effectiveness of off-loading by appropriate footwear, especially in difficult and challenging cases.

Although several studies exist evaluating whole foot pressures, there is a paucity of research examining forefoot and rearfoot plantar pressures. In our unit, we measured forefoot and rearfoot pressures separately and examined their validity in predicting foot ulceration [13]. Ninety patients with diabetes mellitus were examined, and peak pressures under the rearfoot and forefoot were evaluated using the FSCAN mat system with subjects ambulating without footwear [13]. Significant correlations were found between forefoot peak pressures and age, height, neuropathy disability score, VPT, and force applied on the ground while walking. In contrast, reverse correlations were found between rearfoot peak pressures and measurements of neuropathic severity.

Binary regression analysis demonstrated a higher risk of foot ulceration in patients with high foot pressures. However, no association was found for rearfoot pressure. Thus, peak foot pressure measurements of the forefoot, but not the rearfoot, correlate with neuropathy measurements and can also predict foot ulceration over 36 months. Moreover, forefoot pressure correlated with the severity of diabetic neuropathy and limited joint mobility. It is also of interest that a negative correlation was found between rearfoot and forefoot pressures. This finding confirms that there is a transfer of peak pressures from the rearfoot to the metatarsal heads in diabetic neuropathy. Additionally, it indicates an inability of the neuropathic foot to distribute pressure and avoid the development of high pressures that eventually leads to the production of foot ulceration under these areas. Therefore, measurement of forefoot peak pressures rather than the whole foot may be more useful for identifying at-risk patients when designing a screening protocol [13].

Off-Loading the Diabetic Foot: The Role of Footwear

Given the high rate of foot ulceration in at-risk diabetic patients, the need for better preventative methods to off-load the foot cannot be more apparent. The effectiveness of footwear in reducing high plantar pressures has been scrutinized using the optical pedobarograph [5, 50–52]. Several foot pressure studies have examined hosiery and insole materials in the diabetic at-risk population and in patients with rheumatoid arthritis and neuropathy [12, 15, 16, 50–52]. Currently available footwear products are constantly evolving. Thus, the lack of uniform data makes the interpretation of pressure reduction studies challenging in both clinical and research settings.

Hosiery

The use of padded hosiery to reduce foot pressures has been evaluated in the literature [51–53]. In an initial study, the pressure-relieving capacity of specially designed hosiery with padding at the heel and forefoot was tested [51]. A significant reduction in peak plantar pressure, up to 30%, was obtained from diabetic patients who were at risk for ulceration. In a subsequent study, commercially available hosiery, experimental hosiery, and padded socks were evaluated for foot pressure reduction [54]. Ten patients who wore experimental padded hosiery for 6 months were tested with an optical pedobarograph. The experimental hosiery continued to provide a significant reduction in forefoot pressures at 3 and 6 months, although the level of reduction was less than that seen at baseline.

Furthermore, commercial hosiery designed as sportswear was examined and compared with experimental hosiery. Although these socks (medium- or high-density padding) provided a substantial pressure reduction versus barefoot (10.4 and 17.4%, respectively), this was not as great as that seen with experimental hosiery (27%) [52]. Thus, the use of socks designed to reduce pressures on diabetic neuropathic feet may be an effective adjunctive measure for the reduction of foot pressures. While development of fiber technology and padding distribution continues, the currently available high-density socks are perhaps among the best choice of hosiery for protection of the insensate foot from high plantar foot pressures.

In another study, in-shoe foot pressures of patients with at-risk feet were compared with healthy subject foot pressures without shoes using the FSCAN system [14]. Foot pressures were measured under three conditions in each subject. First, subjects were placed directly in the shoes (S) to measure the pressure between the footwear and the sock. Second, the sensor was taped directly to the barefoot (B), and the subject ambulated wearing both footwear and socks. Finally, the footwear was removed, and each subject ambulated wearing only socks (H). The total force and peak pressure under each foot were measured for each condition.

The results demonstrated that the diabetic group had greater peak pressures compared with the controls and that in both groups a significant pressure reduction was found when subjects ambulated with footwear [14]. The study concluded that footwear can offer a cushioning effect and that this property may be further incorporated to design shoewear that can protect against the development of high foot pressures and foot ulceration (Fig. 14.3).

Following this study, the authors prospectively examined the effect of using specially padded hosiery in combination with specially fit footwear on providing in-shoe pressure relief [53]. Fifty patients at risk for foot ulceration were recruited for the study. All of the patients were provided with three pairs of specially padded hosiery and with two pairs of extra-depth footwear or extra-width running shoes. Dynamic foot pressures were measured at baseline with the patients wearing their regular socks alone, regular footwear and socks, padded socks, and the new footwear and padded socks. Foot pressures were measured at baseline and subsequent visits over a period of 30 months (Fig. 14.4).

As initial pressure relief was provided by the new footwear at baseline compared with the patients' own footwear, yet very few differences in peak forces were found among the baseline, interim, and final visits. Moreover, no significant changes in foot pressures were found over a period of 6 months of continuous usage using specifically designed footwear in a group of diabetic patients at risk for foot ulceration. This also illustrates the importance of making simple recommendations of appropriate footwear in patients at risk for foot ulceration in an effort to provide the most suitable environment for such a foot.

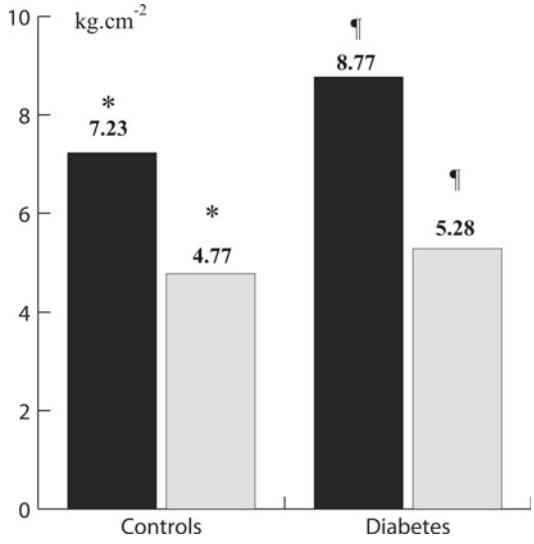

Fig. 14.3 Foot pressure measurement in healthy control subjects and diabetic patients while wearing either their socks alone (*black column*) or both shoes and socks (*white columns*). Foot pressures with socks alone were significantly lower to the ones measured when ambulating with both shoes and socks in both diabetic and healthy subjects (*, ¶: $p < 0.02$) (ref. 14)

Shoewear

Given the potential of shoes and associated modalities to reduce foot pressures in neuropathic feet and healthy subjects, a discussion of the associated off-loading capabilities is warranted. It is anticipated that the use of modern technology may be useful in designing shoes and insoles that will redistribute and reduce foot pressures from areas prone to ulceration.

Shoes are an important consideration for patients at risk for ulceration. They provide protection as a covering for the feet and function as a barrier against toxic substances and thermal extremes. Shoes can also function to decrease plantar foot pressures. For example, noncustom footwear worn by healthy nondiabetic subjects

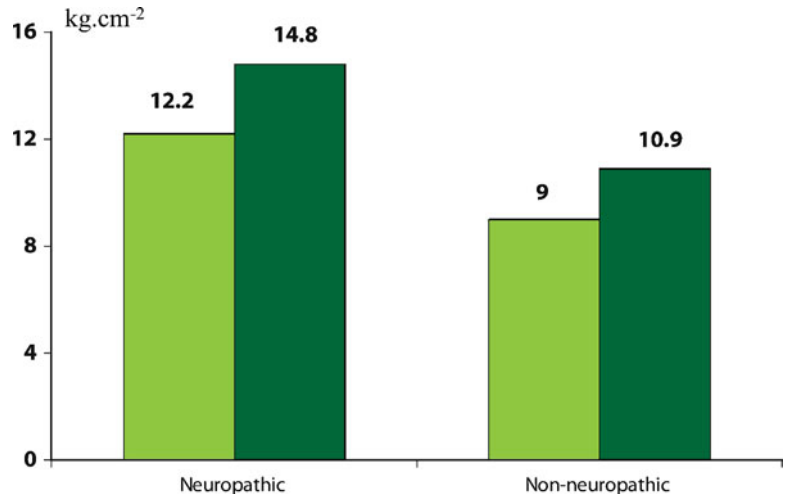

Fig. 14.4 Changes in the peak foot pressures in neuropathic and non-neuropathic patients over a period of 30 months. The pressures at the end of the study (*white columns*) were higher compared to the baseline measurements (*black columns*) in both the neuropathic and non-neuropathic patients (ref. 15)

decreased foot pressures by 30–35% [18]. Moreover, greater foot pressure reductions may be observed in patients with elevated foot pressures wearing shoes compared to walking barefoot.

Healing sandals have been employed to decrease plantar pressures in the diabetic foot [54]. These sandals consist of a postoperative shoe with a thick, soft insole that can be further modified by making the sole rigid with a rocker bottom. The rocker sole is important for the reduction of plantar pressures underneath the forefoot [2, 55]. The soft sole allows for greater pressure distribution beneath the metatarsal heads while the rocker sole alters the mechanics of the forefoot just prior to toe-off, both of which lead to reduced forefoot pressures [55].

The postoperative shoe is another modality used in the treatment of plantar foot ulcerations. This shoe is used quite frequently because of its availability; it provides the patient with a gait-modifying device. There are varying designs of postoperative shoes and some are very hard and have a thin layer of cushioning for the shoe to sit upon. Although it may decrease foot pressures, the best postoperative shoe is only minimally effective in the treatment of foot ulcerations compared with other modalities [54] and is slightly more effective than a canvas shoe [56]. Being flat and having minimal cushioning may actually increase foot pressures, especially for prominences on the plantar aspect of the foot. Therefore, modifications to the sole and insole may further be necessary to enhance the effectiveness of the postoperative shoe. By itself, it is often not a good choice for off-loading a neuropathic prominence.

Additionally, half-shoes have been used with success for plantar pressure reduction [54–56]. These shoes consist of a postoperative shoe with a large wedge heel that extends just behind the forefoot. With a heel of this configuration, the forefoot is kept off the ground. Pressure reduction can be as high as 66% compared with pressures in a baseline canvas shoe [56]. Because of the configuration of the heel which is high and wedged in dorsiflexion, instability when ambulating can be a problem. This instability is even more significant with neuropathic patients.

Fig. 14.5 Running shoes can reduce foot pressures. They are readily available, lightweight, and affordable. The material of the shoe upper is soft and padded on the inside, where it interfaces with the foot. A soft sole will reduce foot pressures along with a soft insole that should be removable to allow for frequent replacement

Therefore, an ambulatory aid, such as a cane or crutches, may assist in walking. It may also make ambulation slightly more difficult which may be a reason for a patient to use it less or to stop using it all together.

Not all shoes relieve foot pressures equally; however, employing materials that significantly reduce foot pressures may prevent the recurrence of ulceration in patients with a prior history of ulceration [56]. Shoes that provide a cushion effect reduce plantar pressures [54, 56]. Leather oxford shoes may decrease plantar pressures in some areas and yet increase pressures in other regions, particularly underneath the lateral metatarsal heads and great toe [56]. Therefore, when purchasing a dress shoe, patients should select a softer sole as opposed to a harder sole, which may not afford as much pressure relief. A dress shoe with a rigid sole can be replaced with a softer sole without dramatically altering the appearance of the shoe. Also, selection of a shoe with a removable insole allows for frequent replacement of worn insoles with a new cushioned insole and results in a greater cushioning effect.

Running shoes are an option for patients with elevated foot pressures and at-risk feet [56–58] (Fig. 14.5). Also, running shoes are less expensive than extra-depth and custom footwear. They provide a readily available option for obtaining

protective shoewear for patients with a reasonably shaped foot. Moreover, running shoes may provide a more cosmetically acceptable alternative to extra-depth or custom shoes. Significant pressure reduction can be expected with running shoes. Thirty-nine subjects were studied to evaluate the pressure-reducing effects of running shoewear [58]. Three groups of thirteen subjects were categorized as having diabetes with neuropathy, diabetes without neuropathy, and with neither diabetes nor neuropathy. Foot pressures were evaluated while subjects were wearing thin socks and compared with those of subjects wearing leather oxford and running shoes. A mean decrease in foot pressures of 31% was noted for all three groups while wearing running shoes compared with wearing the socks alone [58].

In another study, 13 patients with diabetes and neuropathy were evaluated in various types of footwear, including the patients' own leather oxford and extra-depth and running shoes [59]. Running shoes were found to decrease mean plantar foot pressures in comparison with the patients' own leather oxfords by 47% at the second and third metatarsophalangeal joint (MTPJ), 29% at the first MTPJ, and 32% at the great toe [59]. Running shoes are, therefore, a viable option for patients at risk for ulceration. For patients with significant foot deformities and prominences, other options such as custom footwear must be considered.

Different types of shoes provide various levels of plantar pressure relief. A recent study using a running shoe product found a decrease of between 27 and 38% in plantar pressures compared with a leather oxford product [60]. Similarly, another study employing a running shoe demonstrated a reduction of between 29 and 47% in foot pressures compared with leather oxford footwear [61].

Note that athletic shoes may not provide the same pressure relief compared with running shoes. For example, cross-trainer-style footwear may not decrease foot pressures compared with running shoes [62]. Foot pressures in 32 diabetic patients with neuropathy and histories of recently healed ulcerations were examined. Foot pressures were measured in a canvas oxford and compared with those using an extra-depth shoe, an SAS comfort shoe, and athletic cross-trainer shoes. Measurements were obtained with the manufacturers' insole and with a viscoelastic insole for each shoe type. For patients with a history of ulcerations underneath the metatarsal heads, pressure reduction in all three shoe types was relatively similar as compared to foot pressure reduction in canvas shoe [62].

However, for those patients with a history of great toe ulcers, the extra-depth and comfort SAS shoes decreased foot pressures under the great toe while the cross-trainer shoewear actually increased foot pressures in this area as compared to the canvas oxfords. One may surmise that foot pressure reduction between running shoes and cross-training shoes may be different, particularly underneath the great toe. Therefore, patient counseling on the selection and purchase of specific footwear is vital, especially in the marketplace, where the vast choices of footwear available may easily overwhelm a patient not familiar with athletic shoes [62].

Extra-depth footwear is another option for the patient with at-risk feet. The extra space in the toe box is particularly useful for patients with forefoot deformities. Extra-depth footwear also decreases foot pressures significantly [56–58]. The pressure reduction ability of extra-depth shoewear can be further augmented with the use of specially padded socks as discussed previously [59, 60] and insoles [58]. It is the authors' experience that many extra-depth shoes contain a flat insole with minimal cushioning quality. A study evaluating extra-depth shoes demonstrated pressure reduction with the factory insole 16, 27, 19, and 34% at the great toe, 1st MTPJ, 2nd MTPJ/3rd MTPJ, and heel, respectively [59]. With a custom-accommodative insole, the pressure reduction was increased to 33, 50, 48, and 49%, respectively [59]. In a subsequent study, 32 patients with diabetes and a history of ulceration noted a significant reduction in foot pressures using extra-depth shoes when compared with a baseline of the patients' own canvas oxford. When the factory-constructed insole was replaced with a commercially available insole, a further pressure reduction of 4–15% was observed. Therefore, pressure reduction using extra-depth

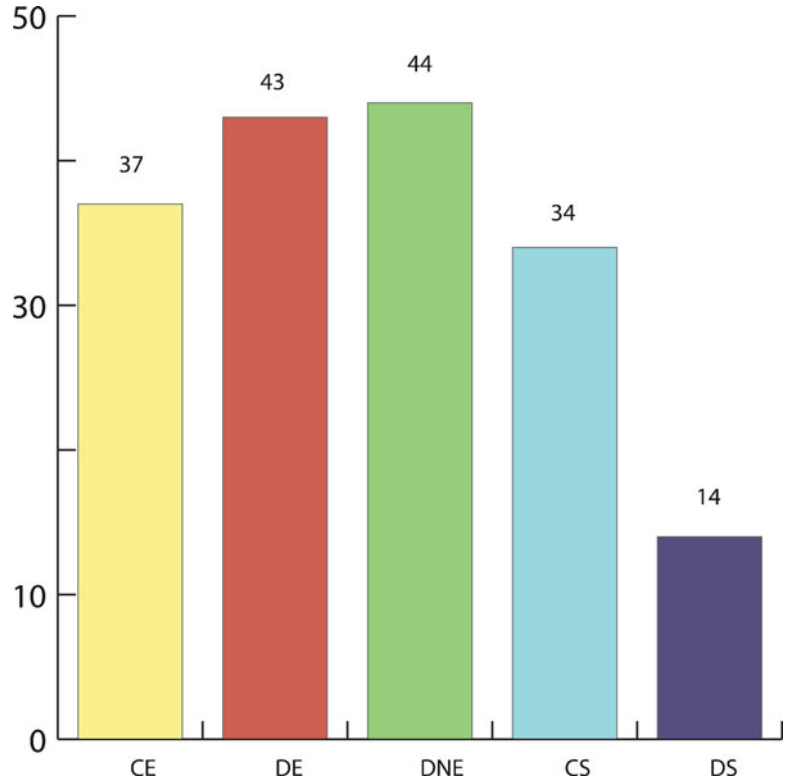

Fig. 14.6 Percentage of foot pressure relief achieved by the athletic shoes in healthy controls who exercised regularly (CE group), type 1 non-neuropathic diabetic patients who exercised regularly (DE), type 1 diabetic neuropathic patients who exercised regularly (DNE), healthy controls who did not exercise regularly (CS), and diabetic patients who did not exercise regularly (DS). The highest pressure relief was achieved in the three first groups who consisted of regularly exercising subjects. These data indicate that proper selection of footwear can result to considerable pressure relief (ref. 60)

shoes can easily be augmented with the use of a readily available insole. The pressure-reducing ability of extra-depth footwear can be further augmented with specially padded socks [47].

In another study, diabetic patients who exercised and those who did not were evaluated to determine what effect aerobic exercise might have on foot pressures with and without shoes [60]. When participants ambulated without their shoes, the peak pressures were highest in group DNE (diabetic non-exercisers). Foot pressures were also higher in groups CE (healthy exercisers), CS (healthy nonexercisers), and DE (diabetic exercisers), probably a result of the increased stress of the foot skin and the subsequent callous formation.

However, when foot pressures were measured wearing shoes, a different picture emerged. The foot pressures were highest in groups CS and DS, intermediate in group DNE, and lowest in groups CE and DE (Fig. 14.6). Those who consistently exercised achieved the highest pressure relief. These differences may reflect the ability of regularly exercising individuals to choose comfortable and good-quality shoewear. In summary, these results indicate that proper selection of footwear can result in considerable pressure relief.

A key component of footwear that may need to be considered is the issue of a rocker bottom sole. This is an aspect that may be considered in addition to insole or orthotic design and material selection, where pressures are relieved in an area of concern and redistributed to the entire foot. A rocker sole, however, is a very important consideration when considering forefoot pressure reduction. Nawoczenski et al. noted that a rocker

sole may be effective in reducing forefoot pressures in patients without neuropathy [55]. It may be the reason that certain running shoes that function this way are effective in reducing forefoot pressures with the stock insole [58, 59]. It has also been advocated when recommending a shoe type for a patient with neuropathic feet. Considerations for prescribing a rocker sole include the "rocker point" which is the point at which the rocker begins and described as a percentage of the distance from the heel when compared to the length of the entire sole. This value has been offered at 65%. The other consideration is the "rocker angle" or the angle from the sole to the tip of the shoe with the apex at the "rocker point" optimally considered to be 23°.

Insoles and Orthotics

Insoles and orthotics are recommended for the prevention of ulcerations in at-risk feet [61–64]. The addition of a material to cushion the plantar aspect of the foot can decrease foot pressures significantly [5]. For example, a 5-mm-thick viscoelastic polymer insole has been reported to reduce foot pressures by approximately 50% [61]. In another study, 4-mm-thick viscoelastic insoles were noted to decrease foot pressures from 5 to 20% above what was observed with stock insoles of extra-depth, comfort, and athletic shoes [30].

Custom orthotics of both the soft and rigid variety are used to decrease foot pressures [63–67]. Heat pressed plastizote™ custom accomodative foot orthoses decrease foot pressures for diabetic patients by 40–50% [65]. Modifications to these insoles by adding arch or metatarsal pads do not increase the pressure reduction significantly [65]. However, rigid materials, such as polyurethane foot orthoses, may reduce plantar pressures by approximately 50% [66]. Rigid orthotics composed of graphite materials decrease pressures underneath the first metatarsal head and medial heel by approximately 30–40% [66, 67].

The FSCAN system was employed to measure dynamic pressures at the shoe–foot interface during normal walking with different orthotics [66]. This study evaluated the efficacy of pressure redistribution with a Plastizote, Spenco, cork, and plastic foot orthosis as compared with a control (no orthotic). Measurements varied upwards to 18% between sensors and changes in stance time of up to 5% occurred between the orthotics and the control conditions. These results demonstrated the inherent measurement variances of the FSCAN system using numerous orthoses.

Although these variances hindered reliability among the orthoses, statistically significant differences in peak pressure between the orthotics were noted. Plastizote, cork, and plastic foot orthoses were beneficial for decreasing pressure in the forefoot, heel, and second through fifth metatarsal regions. However, these orthotics had the potential to increase the plantar pressures in the midfoot region. In conclusion, the results demonstrated that using an orthotic to relieve pressures in one region of the shoe–foot interface may increase pressures over another region of the plantar surface [66].

Viswanathan et al. also evaluated the effectiveness of different insoles in therapeutic footwear. They evaluated neuropathic diabetic patients stratified into four groups. Three of the four groups consisted of patients with therapeutic shoes with insoles, each group differing in the composition of the insole. They were compared to a fourth group of similar neuropathic diabetic patients with nontherapeutic footwear. Foot pressures were measured initially and 9 months later and were noted to be significantly reduced along with the rate of development of new ulcerations as compared to the group wearing the nontherapeutic footwear [67].

Interestingly, not all studies support the use of therapeutic footwear in the prevention of foot ulcerations in those patients at risk. A study by Reiber et al. [68] has demonstrated that therapeutic footwear did not prevent ulceration in their study of diabetic individuals without severe foot deformity. In this study, patients with custom foot insoles fared no better than patients with prefabricated foot insoles and control patients with their usual footwear. All three groups had a similar rate of ulceration. It is important to understand that this does not indicate that therapeutic footwear has less importance than previously thought.

It may play just an important role as ever in patients with severe deformities. It may also mean that the custom insoles in the study were not off-loading the sites of increased pressure any better than prefabricated devices or usual footwear, but this is difficult to ascertain as pressure measurements between groups were not carried out. Perhaps, future studies may investigate the ability of widely dispensed therapeutic footwear to decrease foot pressures by actually measuring foot pressure reduction and correlating this to the ability to decrease the risk of ulceration.

Summary

Several methods of measuring and reducing foot pressures, including their advantages and limitations, have been discussed. Extra-depth footwear, jogging shoes, hosiery, insoles, and orthoses have been shown to decrease plantar foot pressures. Furthermore, these devices can prevent the occurrence and recurrence of foot ulceration. However, when using orthoses or other inserts, care must be taken not to increase pressures over another region of the foot.

In the last 2 decades, the development of intricate computerized systems has revolutionized diabetic foot pressure measurements and made their application possible for daily clinical practice. Foot pressure measurements obtained from out-of-shoe and in-shoe methods may have far-reaching consequences for both research and clinical applications. Moreover, these systems can potentially identify at-risk patients and provide a basis for the implementation of either footwear modifications or surgical intervention. Foot pressure measurement systems are still being developed. Currently, research is in the initial phase of developing methods of measuring in-shoe shear forces. Piezoelectric transducers are currently being evaluated which may be able to measure both vertical and shear forces [69]. In the future, computer systems will hopefully become more widely available and may be employed routinely for diabetic foot management and a variety of foot conditions.

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Proactive Wound Care

15

Adam Landsman and Thanh Dinh

Abstract

In June, 2003, a paper by Sheehan et al. (Diabetes Care 26:1879–82, 2003) caused many physicians to think about the need for proactive wound care. In this paper, the authors demonstrated a pattern of healing in diabetic foot ulcers in which wounds that did not show a significant decrease in size within 4 weeks of standard treatment, had less than a 10% chance of being closed by week 12. As a result, a benchmark was established, whereby one could say with reasonable certainty that in the absence of at least 50% closure after 4 weeks of standard care, a new approach was needed. When wounds fail to close from initial treatments, it is prudent to reassess the wound environment, the condition of the patient, adjust the treatment, and take proactive steps to enhance and stimulate the healing process.

Proactive wound care involves a series of steps to stimulate the wound to progress towards closure. These steps should be broad in their scope, and should focus on the shortcomings of the wound, and on the barriers to healing. Once potentially problematic issues are identified, the wound care specialist should consider the options that they have to gain control and improve the wound environment.

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In June, 2003, a paper by Sheehan et al. [1] caused many physicians to think about the need for proactive wound care. In this paper, the authors demonstrated a pattern of healing in diabetic foot ulcers in which wounds that did not show a significant decrease in size within 4 weeks of standard treatment, had less than a 10% chance of being closed by week 12. As a result, a benchmark was established, whereby one could say with reasonable certainty that in the absence of at least 50% closure after 4 weeks of standard care, a new approach was needed. When wounds fail to close from initial treatments, it is prudent to reassess the wound environment, the condition of the patient, adjust the treatment, and take proactive steps to enhance and stimulate the healing process.

Proactive wound care involves a series of steps to stimulate the wound to progress towards closure. These steps should be broad in their scope, and should focus on the shortcomings of the wound, and on the barriers to healing. Once potentially problematic issues are identified, the wound care specialist should consider the options that they have to gain control and improve the wound environment. Consensus panels have independently and collectively advocated the use of advanced technologies to stimulate wound healing [2].

In this chapter, we focus on the topical wound technologies available, which help to actively change the wound environment, and subsequently stimulate a wound to heal. Nutritional deficiencies, infections, improper or insufficient control of mechanical forces, and ischemia are all critical to the management of diabetic foot ulcers, and are dealt with very thoroughly in other chapters in this textbook. Similarly, negative pressure wound therapy (NPWT) may be used as a tool to stimulate the healing process. However, in this chapter, the focus is on the use of biologically active materials which stimulate measurable biochemical changes in the wound environment. In broad terms, these biologically active materials can be divided into decellularized materials, such as processed collagen bioscaffolds, and materials which contain cellular components such as the biologic skin substitutes and cryopreserved allografts. Whether a decellularized material or a material containing cellular components is chosen, the goal is usually to introduce collagen and/or growth factors to the wound bed, to proactively stimulate the healing process.

Decellularized Collagen Materials and Extracellular Matrix

Among the decellularized collagen materials currently available for the treatment of wounds, there are many differences and many similarities. Regardless of the material chosen, most have focused on producing a product which is easily incorporated into the wound bed, and delivers quantities of collagen sufficient to provide a scaffold for migration of fibroblasts and keratinocytes across the wound surface. The source of the collagen is quite broad, and may originate from a variety of tissues, including human, bovine and porcine skin, intestinal submucosa, equine pericardium, bovine tendon, and others. It can be processed to maintain the native collagen structure, or can be fractionated. It can be cross-linked and/or laminated for strength, or cross-linking can be avoided in order to promote more rapid enzymatic degradation, and faster incorporation. Depending on the tissue type and age, the variety of collagens can be varied as well. For example, fetal tissues may contain a larger percentage of type 3 collagen. However, most of these products predominately contain type 1 collagen.

Frequently, collagen is described as a building block; an inanimate material that provides a scaffold for supporting the growth of the cellular, "living" tissues [3]. However, it is critical to remember that in skin, the reserves of growth factors are typically found in the extracellular matrix [4]. It is true that growth factors, such as PDGF and TGF are formed in platelets, fibroblasts, and keratinocytes, but once formed, they are housed within the extracellular spaces—in the collagen matrix. Once applied, the collagen matrix actively stimulates wound healing by interacting with the adjacent cells to coordinate release of these growth factors, and launching the wound healing cascade.

The characteristics of the collagen being implanted may strongly influence the host-implant interaction. Among the collagen materials used in wound care, there are essentially two scenarios which are typically seen; incorporation and nonincorporation [5]. Nonincorporation occurs when the material is either encapsulated or rejected. In these cases, the collagen is never integrated into the wound bed. Historically, this has been less desirable, as it defeats the purpose of using a collagen bioscaffold, in that the collagen material cannot add to the stimulation of wound closure. Nonincorporation occurs when the material is highly cross-linked, thereby preventing enzymatic degradation and vascular infiltration of the graft. It can also occur when there has been a robust inflammatory response to the material applied.

Incorporation results in a fundamentally different interaction between the host and the implant. Ideally, cells penetrate and populate the matrix and produce proteins and enzymes that break down collagen fibers and reassemble them to replace native tissues. The decellularized collagen materials that retain the largest percentage of extracellular matrix components, with the least amount of cross-linking are most likely to become incorporated in this manner.

In some cases however, another type of incorporation involving resorption occurs. In this scenario, materials may be rapidly broken down, but not in a less beneficial way, resulting in infiltration, inflammation, and replacement with scar tissue [6]. This nonproductive type of incorporation has been primarily associated with certain types of intestinal submucosa laminates, and appears to be highly dependent on the way in which the tissues are processed. In cases where these materials are used to treat wounds, they may simply act as a wound dressing, and eventually become part of a scab which later sloughs off.

Incorporation may also take place with integration followed by progressive degradation. In this case, the material is repopulated with host cells and vasculature, and this phase is followed by a low-grade inflammatory phase which gradually degrades the material and replaces it with new connective tissue [7]. Once it is clear that a material has been incorporated into the wound bed of a host, the process of wound healing is stimulated through a variety of mechanisms. A wound treated with decellularized collagen is seen in Fig. 15.1.

Decellularized Collagen and Extracellular Matrix Stimulates Wound Closure

The series of events leading to wound healing is complex, and collagen found in the extracellular matrix (ECM) plays a critical role in the entire process. The ECM is composed of proteins that form the structural scaffold of all tissues, including the skin. In addition, ECM proteins can regulate cellular behavior by modulation of growth factor activities, or by direct interaction with cellular components of the host tissue [8], resulting in restoration of damaged tissues during the wound healing process.

There are 28 types of collagen, but type 1 collagen is by far, the most common in the skin. Collagen subgroups, such as multiplexins carry glycosaminoglycan chains and are thus also considered proteoglycans. Proteoglycans are found in basement membranes, and in matrices surrounding mesenchymal cells, and proteoglycans play a critical role in a number of signaling functions which lead to modulation of FGF2, VEGF, and PDGF [9].

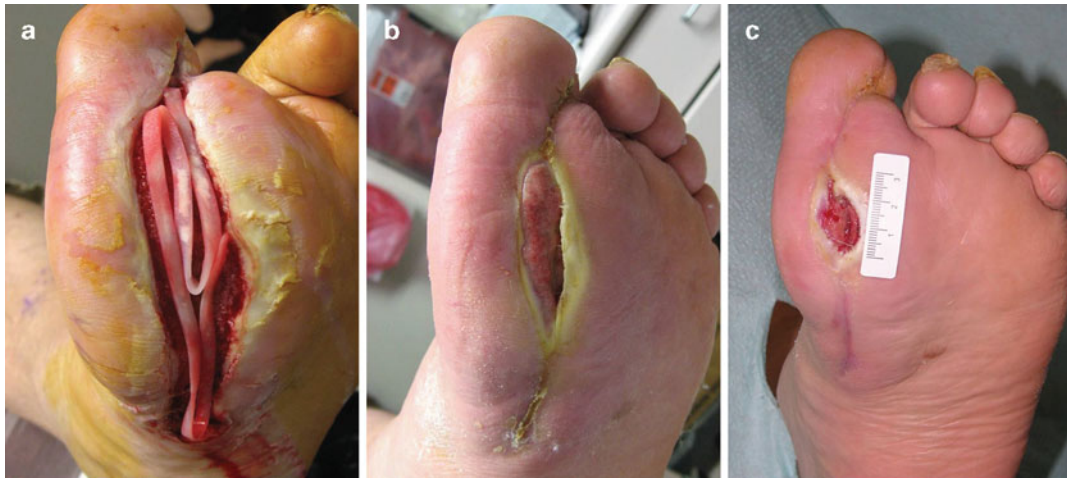

Fig. 15.1 Wound treated with decellularized collagen (Primatrix, TEI, Boston, MA). (**a**) Large plantar wound previously treated with negative pressure therapy. A strip of collagen is applied, and dressed with non-adherent material, and backed with gauze. (**b**) Substantial progress is observed after only 3 weeks. Prior to application of the decellularized collagen, the wound had been unchanged in size for over 1 month. (**c**) Wound is nearly completely closed following a total of three applications of decellularized collagen

Although collagen plays an important role in the closure of wounds, the full ECM is much more complex, and can contribute much more to the process. Aside from collagen and proteoglycans, ECM contains fibronectin, a large adhesive glycoprotein with a variety of functions. After injury, fibronectin is released from blood plasma to the ECM, where it stimulates the release of growth factors and cytokines [9]. Together with fibrin, it provides a provisional matrix to guide fibroblasts and inflammatory cells to the site of injury. In the process, the fibroblasts secrete fibronectin dimers which are organized into a network to form a stable collagen I and III network. Laminins are a family of 16 different types of proteins, also found in the ECM. These are found in the basement membrane of blood vessels, and are critical for re-epithelialization and vascularization of the skin as it is being repaired [10].

ECM plays an important role in the availability of growth factors in wounds. Components of the ECM can actively modify activity of growth factors and cytokines, and can protect growth factors from degradation. Interestingly, ECM can serve as a reservoir for growth factors, where they can be rapidly released when needed. Normal skin can bind FGF-2, TGF-beta, VEGF, and PDGF [4].

Based on this discussion, one can see that collagen provides more than just a scaffold for supporting living cells. In fact, collagen plays a substantial role in helping the body to proactively stimulate healing. It works in concert with the cells of the host tissues to accelerate wound healing. Later in this chapter, data is presented which supports the use of decellularized collagen materials to promote wound closure. Data will also be presented which illustrates the use of cryopreserved allografts that provide a fully matured ECM to the wound bed. But first, the authors will examine bioengineered skin substitutes, and the role they play in the treatment of wounds. These materials are skin-like grafts, grown in the laboratory, and contain living cells (fibroblasts or fibroblasts and keratinocytes) applied to the wound surface.

The Bioengineered Skin Substitutes

Bioengineering skin substitutes emerged to serve as a new way to deliver growth factors and collagen to the wound bed, from an exogenous source. The materials are created in a laboratory, and contain some elements of natural skin. Although most growth factors are stored within

the extracellular matrix, the attraction of implanting living cells which are capable of contributing additional growth factors to the wound bed has wide appeal. Currently, there are two products on the market, DermaGraft and Apligraf, which are widely used, and others in various stages of development.

Dermagraft

Dermagraft is a bioengineered skin substitute that contains allogenic neonatal fibroblasts impregnated on a bioabsorbable polyglactin mesh (Dermagraft, Advanced Tissue Sciences Inc, La Jolla, CA). There are three major production steps in the manufacturing of Dermagraft. First, fibroblasts from human neonatal foreskin are screened, enzymatically treated, and either banked or placed into a tissue culture. Next, allogenic dermal fibroblasts are seeded onto a bioabsorbable polyglactin mesh. Finally, the cells proliferate and produce dermal collagen, growth factors, GAGs, and fibronectin during a 2- to 3-week period.

The final structure is similar to the metabolically active papillary dermis of neonatal skin. Dermagraft contains some growth factors and matrix proteins that are instrumental to wound healing such as: platelet-derived growth factor A (PDGF-A), insulin-like growth factor (IGF), mitogen for keratinocytes (KGF), heparin binding epidermal growth factor (HBEGF), transforming growth factors (TGF-α, TGF-β1, TGF-β3), vascular endothelial growth factor (VEGF), and secreted protein acidic and rich in cysteine (SPARC). The matrix proteins and growth factors remain active after implantation onto the wound bed [11]. No exogenous human or animal collagen, GAG, or growth factors are added.

In addition to providing a variety of growth factors intended to accelerate wound healing, it has been suggested that Dermagraft may help to stimulate angiogenesis, possibly through up-regulating cellular adhesion molecules in response to growth factor stimulation [11]. Preclinical studies in animals indicated that Dermagraft incorporates itself into the wound and becomes vascularized within the confines of the wound bed. Preclinical data also indicated that Dermagraft potentially limited wound contraction and scarring through its influence on the local wound healing process.

Dermagraft is designed to replace the dermal layer of the skin and to provide stimulus to improve wound healing. The histological cross-section shows human collagen fibers arranged in parallel bundles. In clinical practice, Dermagraft is supplied as a 2-in. by 3-in. graft in a sealed plastic bag on dry ice. It must be rapidly thawed and warmed before application on to the wound in a precise manner, in order to avoid injury to the cryopreserved cells. Following appropriate wound bed preparation, Dermagraft can be cut to the wound size or applied in total in a packed fashion. Secondary dressings are used to keep the implant in place and keep the wound moist. Dermagraft acts on the wound by cell colonization and provision of growth factors and cytokines. Because of cryopreservation, the cells can lose some viability and therapeutic effect [12].

Efficacy of Dermagraft in Diabetic Foot Ulcers

A pilot study was performed to assess the efficacy of Dermagraft diabetic foot ulcers for a duration of 12 weeks [13]. Fifty patients were enrolled and divided into four treatment groups. Group A patients received one piece of Dermagraft weekly for a total of eight pieces and eight applications plus control treatment. Group B patients received two pieces of Dermagraft every 2 weeks for a total of eight pieces and four applications plus control treatment. Group C patients received one piece of Dermagraft every 2 weeks for a total of four pieces and four applications plus control treatment. Group D patients received conventional treatment only. Patients in all groups had very similar demographic characteristics. After 12 weeks, group A patients achieved more wound healing than other groups, implying that sequential weekly treatments may be optimal for use with this product. Wound closure in the group A

patients (50%) after 12 weeks was significantly better than the control group (8%, $p=0.03$). There were no reported adverse events in this study.

In follow-up to the pilot study, a large, prospective, randomized control study was conducted to investigate the effectiveness of Dermagraft on diabetic foot ulcers [14]. A total of 281 patients were enrolled at 20 centers. Patients were randomized to receive either Dermagraft weekly for a total of eight applications or only conventional wound care. One-hundred and twenty-six patients were enrolled in the standard wound care group, with 31.7% healing rate by the end of week 12. One-hundred and nine patients received Dermagraft treatment, resulting in a 38.5% healing rate by the end of week 12. The healing rates between the two groups was found to be a statistically nonsignificant result ($p=0.14$).

Further analysis of the data revealed that a specific range of metabolic activity of Dermagraft was associated with higher complete healing rate by week 12 [15]. Seventy-six patients received metabolically active products at least at the first application, and 48.7% of these achieved wound healing by week 12 ($p=0.008$). Sixty-one patients received metabolically active products at the first two applications and as well as many of subsequent applications, and 50.8% of these patient had complete wound closure by week 12 ($p=0.006$). Thirty-seven patients received the correct metabolically active products at all applications, and they achieved the highest healing rate of 54.1% by week 12 ($p=0.0067$). A supplemental study using Dermagraft within the therapeutic range reported healing rates of diabetic foot ulcers above 50% at 12 weeks [16].

A subsequent study involving more centers and larger patient population was concluded recently. In a randomized, controlled, multicenter study at 35 centers, 314 patients were randomized to either the Dermagraft treatment group or control group (conventional therapy) [17]. Except for the application of Dermagraft (applied weekly for up to 7 weeks), treatment of study ulcers was identical for patients in both groups. All patients received pressure-reducing footwear and were allowed to be ambulatory during the study.

The results demonstrated that patients with chronic diabetic foot ulcers of >6 weeks duration experienced a significant clinical benefit when treated with Dermagraft versus patients treated with conventional therapy alone. With regard to complete wound closure by week 12, 30.0% of Dermagraft patients healed compared with 18.3% of control patients ($p=0.023$). The overall incidence of adverse events was similar for both the Dermagraft and control groups, but the Dermagraft group experienced significantly fewer ulcer-related adverse events.

Apligraf

Apligraf is a composite graft comprising a cultured living dermis and sequentially cultured epidermis, derived from neonatal foreskin (Graftskin, Organogenesis Inc., Canton, MA). Apligraf is a bilayered skin construct and consists of four components: extracellular matrix, viable allogenic dermal fibroblasts, epidermal keratinocytes, and a stratum corneum. The ECM of Apligraf consists of type I bovine collagen (acid-extracted from bovine tendon and subsequently purified) organized into fibrils and fibroblast-produced proteins. This matrix promotes the ingrowth of cells, provides the scaffold for the three-dimensional structure of Apligraf, and provides mechanical stability and flexibility to the finished product.

The dermal fibroblasts produce growth factors to stimulate wound healing, contribute to the formation of new dermal tissue, and provide factors that help to maintain the overlying epidermis. The epidermal keratinocytes form the epidermis. They produce growth factors to stimulate wound healing and achieve biologic wound closure. The stratum corneum provides a natural barrier to mechanical damage, infection, and wound desiccation. Despite containing allogeneic proteins and cells, Apligraf has not been shown to produce an adverse host response. It has been speculated that this is the result of the lack of antigen promoting cells common to the tissue engineered products.

Apligraf is processed under aseptic conditions and thus requires similar handling. Blood samples of the maternal parent of the foreskin donor is tested and compared to normal ranges. Test for many infectious agents are performed and include anti-HIV virus antibody, HIV antigen, Hepatitis, Rapid Plasma Reagin, Glutamic pyruvic transaminase, Epstein-Barr, and Herpes Simplex. The cells are also tested for many infectious agents and also for any evidence of tumorigenic potential.

Apligraf is supplied as a circular sheet approximately 3 in. in diameter (44 cm^2) in a plastic container with a gel-cultured medium. Apligraf looks and feels like human skin. Histological sections showed that Apligraf lacks blood vessels, sweat glands, and hair follicles and contains cytokines present in human skin. Apligraf is shipped in a sealed plastic bag that can be kept at room temperature for up to 5 days. Once the bag is opened, the product must be applied within 30 min. The color of the gel medium will change to indicate when the product is no longer usable. The epidermal layer is closest to the lid of the plastic container, and has a matted or dull finish. The dermal layer rests on the insert membrane closest to the gel medium, and has a glossy appearance.

Apligraf can be trimmed to size and applied to the ulcer with the dermal layer in contact with the wound bed. However, the wound bed should first be debrided extensively of all necrotic and nonviable tissue. Apligraf can then be applied with overlap of the product over the wound edge onto normal surrounding tissues without causing any harm. Apligraf can be "meshed" to cover a larger wound and can be sutured in place to ensure the implant does not shift off the target wound. Secondary dressings are used to keep the implant in place and to maintain a moist wound environment. A wound treated with Apligraf is seen in Fig. 15.2.

Efficacy of Apligraf in Diabetic Foot Ulcers

In a pivotal multicenter, prospective, randomized control clinical trial, the efficacy of Apligraf in the treatment of chronic diabetic foot ulcers was evaluated [18]. Two-hundred and eight patients enrolled in 24 centers across the country. The efficacy of the treatment was studied for 12 weeks, followed by another 3 months of safety follow up. Ninety-six patients were randomized to control group, receiving saline moistened gauze treatment in addition to good wound care and offloading techniques. One-hundred and twelve patients were randomized to the treatment group receiving Apligraf once a week for the first 4 weeks with a maximum of five applications. After week number 4, patients in the treatment groups received similar dressing regiments as the control group.

The Apligraf-treated ulcers quickly showed difference in treatment compared to the control group. After 4 weeks, 20% of patients who received Apligraf achieved wound healing compared to 3% in the control group. After 8 weeks, 45% of patients who received Apligraf treatment healed their ulcers compared to 25% of the control group. By the end of week 12, 56% (63/112) of Apligraf-treated patients had complete wound closure compared to 39% (36/96) of the control ($p = 0.0026$). Furthermore, among the patients that had complete wound closure, the median time to 100% wound closure for Apligraf group was 65 days compared to 90 days for the control group. The recurrence rate at 6 months was similar in both treatment groups, with 8% (5/63) of the Apligraf-treated patients reulcerating compared to 17% (6/36) of the control group.

Safety data also revealed that patients treated with Apligraf had a lower incidence of osteomyelitis and lower frequency of amputation. This is most likely attributed to the fact that the longer a wound remains open, the greater the opportunity for an infection to develop. The incidence of adverse events was similar in the two treatment groups during the study.

Subsequent studies of Apligraf in diabetic foot ulcers have yielded similar results. In a study evaluating 41 consecutive diabetic and pressure foot ulcers, Brem et al. reported increased wound healing following the application of Apligraf [19]. In 2010, a multicenter, prospective, randomized, controlled, open label study conducted in

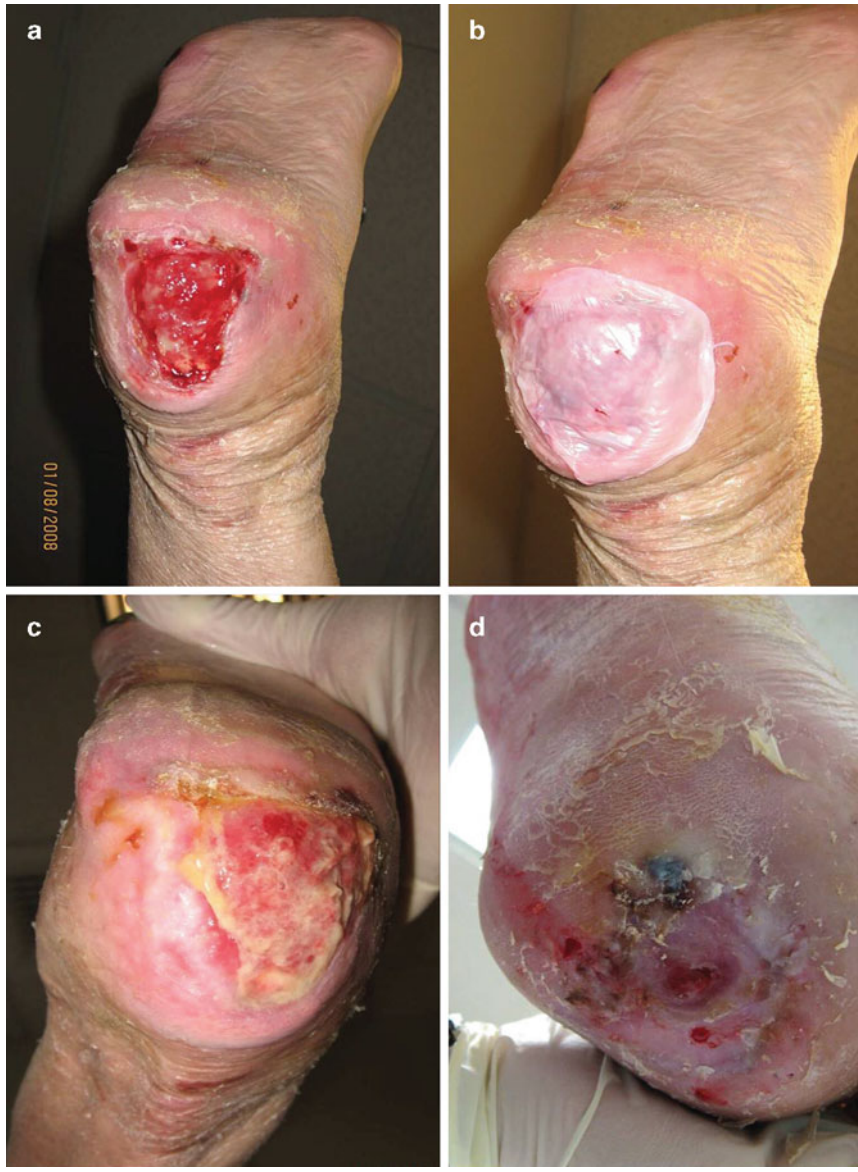

Fig. 15.2 Wound treated with Apligraf (Organogenesis, Canton, MA). (**a**) This is a large heel decubitus ulcer which has been debrided and is ready for application of Apligraf. (**b**) The Apligraf is laid over the wound. We covered this with a non-adherent moist dressing. (**c**) Formation of neodermis (*yellowish material*) is present, and the Apligraf appears to have been well incorporated. (**d**) The wound goes on to heal after three applications of Apligraf

Europe and Australia, treated 72 diabetic foot ulcers with Apligraf. Apligraf-treated ulcers exhibited 55.2% complete wound closure by 12 weeks, compared to only 34.3% of control subjects. When separated and compared by geographic location, the European and Australian groups demonstrated similar results between Apligraf and control groups, lending robust evidence in the efficacy of Apligraf for the treatment of diabetic foot ulceration [20].

Clinical Application

The exact mechanism of action of bioengineered skin substitutes is still under much discussion and research. It is believed that bioengineered skin substitutes act as a "smart matrix" by inducing the expression of growth factors and cytokines that contribute to wound healing [21]. It is postulated that the donor allogeneic cells from bioengineered skin substitutes are responsible for the delivery of growth factors and cytokines that serve to "correct" the impaired healing. These growth factors and cytokines include interleukin-1, interleukin-3, transforming growth factors α and β, and basic fibroblast growth factors critical to the wound healing process [22].

What remains unclear is how long these donor allogeneic cells remain active in the wound site. Using polymerase chain reaction analysis, Phillips et al. detected allogeneic donor cell DNA after the initial month of grafting [23]. However, the allogeneic DNA did not appear to persist after 2 months of grafting. Thus, repeated application of the living skin equivalents may be necessary to ensure the presence of growth factors and cytokines essential to wound healing.

Some bioengineered skin substitutes may become vascularized with time and lead to graft integration analogous to autologous skin grafting. Using laser Doppler imaging, Newton et al. assessed blood flow in seven diabetic foot ulcers treated with eight applications of Dermagraft on a weekly basis [24]. It was demonstrated that blood flow increased by an average of 72% at the base of five out of seven diabetic foot ulcers. This angiogenesis may bear some responsibility for the effectiveness of bioengineered skin substitutes in the treatment of diabetic foot ulcers.

Complications with the use of bioengineered skin substitutes have been minimal if not rare. It was initially feared that immune reaction from the host may lead to rejection of the graft. However, rejection of the bioengineered skin substitutes or development of immune sensitization does not appear to be a problem. It is believed that this may be due in part to the fact that neonatal fibroblasts lack the HLA-DR surface antigens, which are responsible for generating allograft rejection [25].

As in many studies, patients with severe medical conditions such as end stage renal failure on dialysis are often excluded. Anecdotally, some of the authors' diabetic patients who had end stage renal disease on hemodialysis were able to achieve complete wound healing on their chronic ulcers using Apligraf in addition to normal good wound care and offloading technique.

What Does the Literature Tell Us About Proactive Wound Care Modalities?

Arguably, the approval of Bercaplermin (PDGF-bb), DermaGraft and Apligraf brought proactive wound treatment options to the forefront. These three products demonstrated that there were wound treatments that could stimulate an otherwise quiescent wound to begin healing. However, the use of skin allografts pre-empted these treatments by more than a decade, and may provide many of the same benefits, including collagen and ECM. Decellularized collagen products also made a substantial difference in stimulating wounds to heal, and will be examined here as well. Although there has never been a strong head-to-head comparison of these materials, we will attempt to compare them by reviewing the literature available on each.

One difficulty that exists when comparing various proactive wound treatments is that the criteria for each study may differ substantially. Concomitant treatments, various off-loading strategies, and the location and class of wound may all vary, resulting in a wide variety of outcomes, even with the same product. Nonetheless, some of the larger, more statistically sound studies do provide some insight as to the type of results one can reasonably expect. One fact that becomes apparent is that the proactive wound care modalities do make a difference. In nearly every study, the addition of growth factors, and/or collagen cause wounds to close more frequently and more rapidly. Each proactive material may vary in the specific components delivered, with some providing primarily collagen, while others provide living cells. Human skin allografts can provide a combination of all of the above when properly harvested and preserved.

Table 15.1 Clinical outcomes with proactive wound treatments

Material	Author (references)	Study type	*n*	Initial wound size (cm^2)	% Closed at 12 weeks	Average number of treatments
Apligraf	Veves et al. [18]	Randomized, prospective, control	208 pts. 112 with Apligraf	2.97 (3.10)	56%	3.9 grafts
Apligraf	Steinberg et al. [20]	Randomized, prospective control	72 pts. 32 with Apligraf	3.04 (2.03)	51.5%	1.8 grafts
DermaGraft	Pollak et al. [14]	Randomized, prospective control	281 pts. 109 with DermaGraft		38.5%	
DermaGraft	Marston et al. [17]	Randomized, prospective control	314 pts. 130 with DermaGraft	2.31 (0.75–16.7)	30%	Up to 8 grafts
DermGraft	Gentzkow et al. [13]	Randomized, prospective control	50 pts. 25 with DermaGraft		50%	Up to 8 grafts
DermaGraft	Gentzkow et al. [26]	Randomized prospective control	281 pts. 109 with DermaGraft		51% (healing rate dependent on graft viability)	Up to 8 grafts
Regranex	Wieman et al. [27]	Randomized prospective control	382 pts. 123 with 100 μg Regranex	2.7 (±3.45)	48% (at 20 weeks)	Gel applied daily
TheraSkin	Landsman et al. [14]	Retrospective consecutive	188 pts. 54 with DFU's	6.2 (±11.8)	60.38%	2.03 (±1.47)

Proactive wound care evolved from the addition of growth factors captured from the patient's own serum, spun down to isolate growth factors such as PDGF. Bercaplermin (Regranex) was the first commercially available bioengineered growth factor (rhPDGF-BB). It was shown to enhance wound closure, and was believed to be beneficial as a supplement to natural PDGF in patients with chronic wounds. On average, there was a 50% in the wound closure rate after 20 weeks.

Apligraf and DermaGraft are probably the two most complex bioengineered skin substitutes. Both products contain living cells and both have satisfied the Food and Drug Administration's rigorous PMA process (pre-market approval) for the treatment of diabetic foot ulcerations. Numerous studies have been conducted with each product, and some of the most notable studies are summarized in Table 15.1. Most of these studies demonstrate around 50% closure at 12 weeks, using various numbers of grafts, depending on the study designs.

Collagen bioscaffolds form a matrix upon which the host cells can migrate. These scaffolds are distinguished from one another based on the donor tissue, and source. Human skin, bovine skin, equine pericardium, bovine tendon, porcine intestine, and others differ based on the proprietary processes for decellularization, degree of cross-linking, thickness, and type of collagen present.

The relative benefits of one type of collagen preparation versus another is widely debated, and there have been no statistically significant comparisons made to date. However, certain trends have emerged, and this may help the practitioner to select one type of collagen over another.

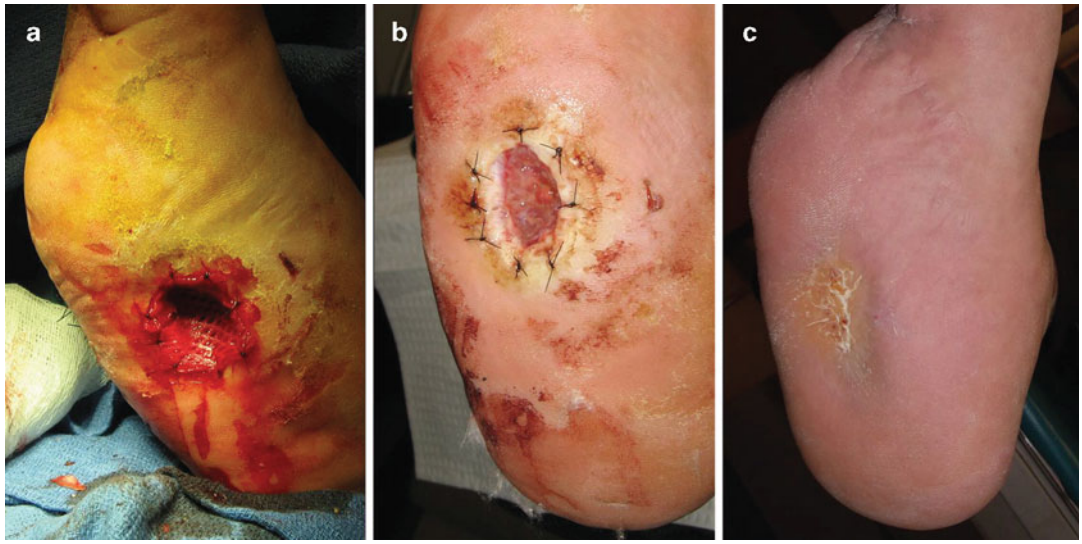

Fig. 15.3 Wound treated with TheraSkin (Soluble Systems, Newport News, VA). (**a**) This large wound was associated with Charcot changes, and had been present for over a year. It extended down to the muscle layer, and had not responded to prior treatments with other biologics. This photo shows how the TheraSkin is stitched in place. It is handled essentially the same as a fresh split thickness skin graft. A non-adherent, absorbent dressing was applied after the graft was applied. (**b**) In this picture, you can see the extensive incorporation of the TheraSkin in to the wound bed. (**c**) The wound goes on to close after two applications of TheraSkin

Cross-linking is usually used to add strength to the grafts, but this may also diminish incorporation, as the cross-linking process limits the ability of collagenase to act on the graft, and may reduce penetration of cutting cones necessary for vascular infiltration.

One distinct advantage associated with decellularized collagen products is the ability to implant it beneath the skin surface, since the antigenic aspects of the collagen have been removed. This makes it a good choice for deep tunneling wounds, and for fat pad augmentation.

Among the proactive materials, there is none which are more similar to real skin, then the cryopreserved human skin allografts. In the 1990s, when fear from AIDS and other communicable diseases such as hepatitis were at their peak, the use of human allografts started to decrease. Today, allografts are viewed in a much different light. The risk of infection from a contaminated graft is much less than 1:1 million, and new techniques for harvesting, screening, and cryopreservation result in a product that is more complete then the bioengineered skin substitutes, is readily available, and costs less than half of the laboratory-fabricated products.

In addition to the cost benefits, there is strong clinical evidence to support its use. A recent retrospective study involving 188 patients treated with TheraSkin (Soluble Systems, Inc., Newport News, VA), demonstrated a healing rate of approximately 60% in the first 12 weeks, and required an average of two grafts for most wounds, ranging from 1 to 9.3 cm^2 [28]. Although there are strong similarities between the bioengineered skin substitutes and skin allografts, the collagen content is much greater in human allografts [29], and the presence of a fully developed ECM also differentiates these materials. An example of a wound treated with TheraSkin is seen in Fig. 15.3.

Conclusions

Proactive wound care has evolved in response to the need for a more aggressive approach to management of diabetic foot ulcers. Essentially, the longer a wound is open, the harder it is to close, and the greater the risk for infection. For a variety of reasons, ranging from excessive mechanical pressure to poor nutritional status, chronic wounds can develop which are difficult to close. Wound care specialists have recognized this difficulty, and have created numerous ways to stimulate the healing process. Debridement is a critical element in the management of diabetic foot ulcers, because it reduces periwound mechanical pressures, reduces the presence of necrotic material and bacteria, and converts the chronic wound in to an acute one.

When more traditional methods fail to stimulate a wound to close, proactive techniques are utilized to introduce growth factors and collagen. Proactive treatments bring some essential missing items to the wound bed, and trigger a cascade of events leading to wound healing. Growth factors stimulate angiogenesis, mitogenesis, and chemotaxis. Collagen is laid down to create a scaffold for cellular migration. As the complexities of wound closure become more apparent, the need for more efficient proactive treatments will evolve. Table 15.1 summarizes the outcomes seen from several of the clinical studies discussed in this chapter.

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Local Care of Diabetic Foot Ulcers: Assessment, Dressings, and Topical Treatments

16

Sarah Elder, Oscar M. Alvarez, and Thanh Dinh

Abstract

The ideal wound environment for the diabetic foot ulcer has historically been described as moist, a trait important to wound healing. However, besides that single characteristic, there is limited evidence to identify a single wound care product that can be described as optimal and universally appropriate for all diabetic foot ulcers. Instead, unique characteristics of the wound may influence the wound dressing selection. Factors such as amount and type of drainage, size, depth, type of ulcer, and condition of the surrounding skin may help guide the wound care provider in selection of the proper dressing. Furthermore, as the wound heals or stalls, reassessment with subsequent change in wound care dressing may result. Finally, due to the chronicity of these types of ulcers, cost may also need to be considered.

Keywords

Ulcer assessment • Ulcer measurement • Wound dressing • Growth factor therapy • Antiseptic wound cleansers • Negative pressure wound therapy • Low-frequency ultrasound • Electrical stimulation • Wound culture

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Introduction

The ideal wound environment for the diabetic foot ulcer has historically been described as moist, a trait important to wound healing. However, besides that single characteristic, there is limited evidence to identify a single wound care product that can be described as optimal and universally appropriate for all diabetic foot ulcers. Instead, unique characteristics of the wound may influence the wound dressing selection. Factors

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such as amount and type of drainage, size, depth, type of ulcer, and condition of the surrounding skin may help guide the wound care provider in selection of the proper dressing. Furthermore, as the wound heals or stalls, reassessment with subsequent change in wound care dressing may result. Finally, due to the chronicity of these types of ulcers, cost may also need to be considered.

There are numerous commercially available wound care products on the market. These products offer many benefits including: a moist wound environment, antimicrobial activity, absorption of excessive exudate, diminishment of inflammatory cytokines toxic to the healing process, promotion of growth factors integral to wound healing, and debridement of necrotic and fibrotic tissue. It is important to note that while wound care dressings may provide all the benefits just described, they will not off-load the pressure from the wound site nor can they replace antibiotic therapy in the face of wound infection.

In this chapter, we discuss (1) ulcer assessment and measurement; (2) currently available wound dressings and their individual characteristics; (3) negative pressure therapy, electric stimulation, and low-frequency ultrasound in wound management; and (4) when to perform wound cultures. Living skin equivalents as well as collagen dressings are discussed in another chapter in this book.

Ulcer Assessment and Measurement

A thorough assessment of the patient and the foot ulcer is essential in the design of an effective standardized program for local wound management. Ulcer assessment should guide management principles by helping to determine whether the wound is infected, whether light or heavy sharp debridement is indicated, what type of supportive care may be needed, approximately how long it will take to heal, and what types of dressings should be used as healing progresses.

A physical exam, detailed history, and diagnostic procedures designed to rule out osteomyelitis and ischemia help to determine the etiology of the ulcer. The most common ulcer etiology in the diabetic patient is neuropathy [1]. Diabetic neuropathy (not peripheral vascular disease) accounts for approximately 60% of all foot ulcerations. Therefore, the majority has adequate circulation and heals with sensible local management coupled with effective off-loading to reduce pressure and friction. At times, diabetic foot ulcers (initially caused by neuropathy) are complicated by other disease conditions that affect the healing process. Most common complications in the diabetic include peripheral vascular disease and chronic venous (or lymphatic) insufficiency [2].

Each ulcer should be classified by wound morphology, severity, and location. In Table 16.1, a format for ulcer assessment is presented that incorporates steps that correspond with all levels of the widely used (but less comprehensive) Wagner [3] and Pecoraro et al. [4] wound classifications. A description of wound and limb appearance, including edema, erythema, exudate, granulation, and the presence of fibrin or nonviable tissues should be recorded. An accurate history of the wound, such as duration of nonhealing and previous (local and supportive) treatments, should also be included. Ulcer area, depth, and degree of undermining should be recorded at weekly intervals and compared in order to evaluate compliance and the treatment approach.

Imaging of the ulcer with radiographs may also be helpful to exclude the presence of osteomyelitis and identify any significant osseous deformities that may cause delays in the normal wound healing process. Radiographs may reveal signs consistent with infection, such as subcutaneous gas, cortical erosions suggestive of osteomyelitis, and may also expose surprise findings, such as foreign body, fractures, or Charcot neuroarthropathy. When radiographs are equivocal for osteomyelitis, but the clinical presentation is strongly suspicious, further imaging with bone scans, magnetic resonance imaging, or bone biopsy may be warranted.

Thorough surgical debridement should be performed at the initial visit provided that there is no evidence of ischemia [5]. This initial (heavy) debridement includes the removal of all nonviable tissues, elimination of undermining, and cutting back to bleeding at the wound margin. Following initial debridement, the wound should

Table 16.1 Diabetic foot ulcer assessmenta

Wound parameters		Severity/descriptions	
Periwound erythema	None: blanches on digital pressure	Mild: nonblanching, may or may not be warm	Marked: nonblanching, warm to touch, with edema
Periwound edema	None	Mild	Marked
Wound purulence	None: exudate is clear, no odor, no pain	Mild: slightly viscous exudates, may be some odor, there could be pain with pressure	Marked: viscous, exudates, heavy drainage, odor, pain with pressure
Wound fibrin: nonviable tissue	None	Mild: covering <50% of the wound bed	Marked: covering >50% of the wound bed
Lower leg edema: localized, pitting, accumulation of interstitial fluid	None	Mild: pretibial digital pressure leaves small but rebounding depression	Marked: pretibial pressure leaves persistent depression
Brawny edema: hemosiderosis, CVI	None	Mild: appears in a limited area, no lipodermatosclerosis	Marked: involving ankle and calf with lipodermatosclerosis
Wound granulation	None	Mild: beginning to fill in, covering <50%, no epithelialization	Marked: covering most of the wound >50% showing signs of epithelialization
Pedal pulses (using hand held Doppler)	Monophasic sounds, ABI < 0.70	Biphasic sounds, ABI > 0.70	Three pulse sounds, ABI > 0.80
Wound measurement	Surface area obtained by tracing the perimeter	Depth: measure with probe at 90° angle to normal skin	Undermining: measure with probe the deepest part of any tunneling or shearing

Data from: Pecoraro, Reiber: *Wounds* 2:65–73, 1990 and Wagner FW Jr: A classification and treatment program for diabetic neuropathic and dysvascular foot problems, in *American Academy of Orthopedic Surgeons: Instructional Course Lectures,* vol 28, Mosby Yearbook, Inc. St. Louis, MO, 1979

[a]Adapted from Allvarez, Gilson, Auletta local aspects of diabetic foot ulcer care in: *The diabetic foot* (Eds Levin, O'Neal, Bowker) Mosby Yearbook, Inc, 1993, p. 260

be reexamined and probed to accurately determine depth and tissue involvement. At each follow-up visit, additional light debridement should be performed to remove callus surrounding the ulcer, eliminate any undermining and entirely exposing the wound margins.

With the ability to accurately predict healing outcomes [6–9], accurate and reproducible wound measurements have become increasingly important. Most clinicians measure wound length and width with a ruler while depth is usually measured with a probe. Those more specialized, measure wounds by tracing the perimeter to determine surface area. Most techniques work well if the wounds are measured by the same individual, using the same measurement parameters. However, if wound measurements are performed by different clinicians the inter-rater reliability can vary as much as 50% [10]. More recently, more objective noninvasive wound measurement systems have become available. These include high-resolution ultrasound (HRUS), digital photo software programs, and tracing programs that simultaneously measure wound surface area [10, 11]. Examples of wound measurements obtained with HRUS (Wound MappingTM), digital photography software (PicZarTM), are presented in Fig. 16.1.

Wound Dressing Function

Until the mid 1900s, wound dressings were basically all the same. They consisted of woven textile fibers whose primary function was to cover the wound, contain (staunch) bleeding, and conceal the wound from the outside environment. The first published scientific confirmation that

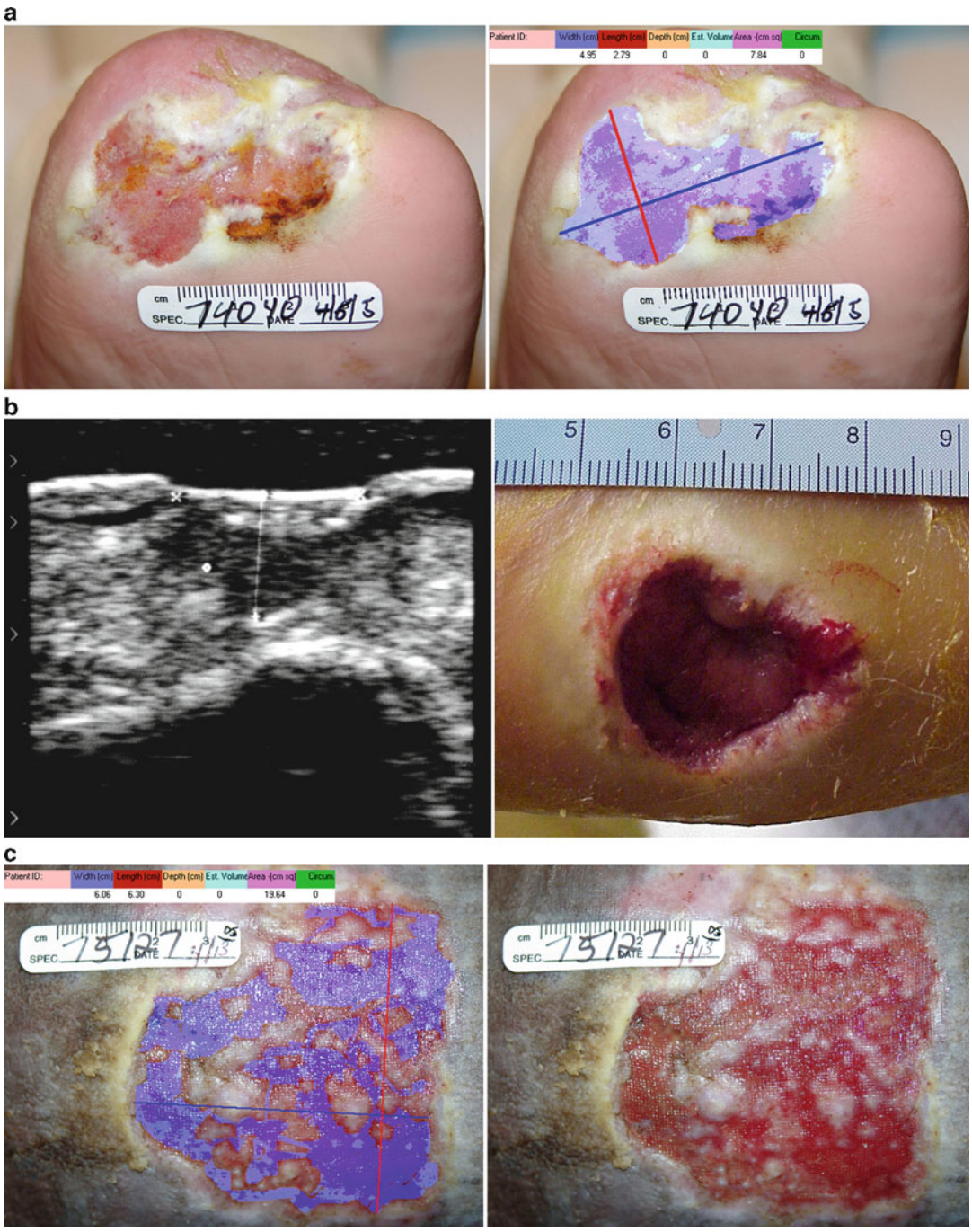

Fig. 16.1 (**a**) Neuropathic foot ulcer measured on digital photographs using digital planimetry software. (**b**) High resolution ultrasonography provides noninvasive, objective, accurate measurements for deeper wounds and allows for examination of undermining and tunneling (*Reprinted from Wendelken, M, Markowitz, L, Patel, M, Alvarez, OM: Objective, noninvasive wound assessment using b-mode ultrasonography. Wounds 2003;15(11)1–10.*). (**c**) For partial thickness wounds like this, healing venous ulcer traditional measurements such as tracings are problematic and inaccurate. With digital planimetry software, the epithelial islands can be easily seen and traced to obtain accurate and reproducible serial measurements of surface area

wounds healed faster in an environment where moisture was retained and crust formation prevented was in 1948. A Norwegian dermatologist, Oscar Gilje noticed that if he covered venous ulcers with strips of adhesive tape spaced apart by 3 mm, the portion of the ulcer covered by the tape epithelialized faster. He replicated these tests in a clinical study involving 23 patients with venous ulcers. Fifteen patients (65%) healed in 12 weeks [12]. These first scientifically controlled studies of moist wound healing beneath occlusive adhesive tape ushered in the age of scientific exploration of wound dressings. In the early 1960s, research by George Winter initiated the concept of an optimal local environment for wound healing and an awareness that the wound dressing could have an interactive role in healing by creating and maintaining such an environment [13]. Winter's studies in 1962 compared the effects of a moist wound environment (with an occlusive dressing) to a dry wound environment (by air exposure) on the epidermal resurfacing of shallow wounds in domestic pigs. His studies demonstrated that reepithelialization occurred twice as fast under a moist environment, where a crust (scab) was unable to form. Although at first skeptical of Winter's findings, thinking that an occlusive environment would result in infection, Himman and Maibach, replicated Winter's studies in human subjects. Their studies published in the Journal *Nature* in 1963 confirmed Winter's results [14]. This awareness precipitated an evolution of wound dressings to interact with the wound to provide an ideal environment for repair.

Despite the many years of favorable results with moist dressings, much work in wound care practice is still not evidence-based. Taking the research and putting it into practice is a goal that still needs to be filled. Even with the tremendous number of new wound care products on the market today gauze continues to be the de facto wound dressing. Studies over many years clearly show that a dressing that retains moisture (enough to prevent crust formation) allows wounds to heal faster, are at less risk for infection, require fewer dressing changes and is also associated with less pain [15, 16]. Contrary to concerns, the moist (occlusive) environment created by occlusive dressings does not lead to increased infection rates. In fact, a retrospective analysis of the literature found a decrease in the incidence of wound infection (on both acute and chronic wounds) with the use of occlusive dressings [17].

Traditional and Advanced Wound Dressings

Today, there are nearly 200 product manufacturers marketing hundreds of brands of traditional (woven and nonwoven) and advanced wound dressings [18]. Combined there are thousands of wound dressings available today. For purposes of reimbursement, dressings have been positioned in several product categories (generally based on the structure or composition of the dressing). Dressing categories include: gauze, impregnated gauze, nonwoven sleeve dressings, transparent films, foams, hydrogels, hydrocolloids, alginates, collagen or extracellular matrix type, superabsorbents, hydrofibers, hydropolymers, medicated dressings, and combination products (Table 16.2). The following section describes the category and our experience with use in diabetic foot ulcers.

Moist gauze has traditionally been used as the control arm in most diabetic foot ulcer healing trials. Moist to moist gauze dressings and effective off-loading is considered standard care for diabetic (neuropathic) foot ulcers [19]. The dressing regimen consists of daily dressing changes with dry gauze as the secondary dressing and anchored with an adhesive tape or bulky rolled gauze bandage. This dressing regimen is useful for uncomplicated superficial ulcers that can be off-loaded easily with a healing sandal and the use of crutches. It should be avoided in large exudative ulcers, if it affects the fit of the treatment shoe and with the use of a total contact cast.

Non-woven dressings, such as sleeve dressings or Telfa® nonadherent brand dressings can serve the role of gauze. Since these dressings are not very absorptive the same rules apply as when using gauze. Nonwoven island dressings with an

Table 16.2 Wound dressing category, type, and clinical evidence

Category	Characteristics	Advantages/ disadvantages	Product examples	Evidence/research support
Moist gauze	Saline moist gauze is applied damp and overlapped with dry gauze. It maintains a moist environment depending on the secondary dressings and tape used	Can cause maceration, does not provide a barrier to exogenous bacteria	Gauze sponges 2×2 and 4×4	Moist-to-moist saline gauze has been used as the control regimen in most clinical trials. The mean incidence of healing in a 12-week period for the control patients (treated with moist gauze) in these studies was 30% [19, 64–66]. 35% of 127 patients treated with moist gauze and placebo gel healed in 20 weeks [67]. 29% of 21 patients treated with saline gauze healed in 20 weeks [68, 69]. From a retrospective analysis, the probability of developing an infection was 6% [70, 71]
Nonwoven/ absorptive/ composites	Multilayer wound covers that provide semi-adherent or nonadherent layer, combined with absorbent fibers, such as cellulose cotton or rayon	Designed to minimize adherence and manage slight amounts of exudates, can cause maceration, is not a barrier to exogenous bacteria	Curad® Telfa® pads Curity® abdominal pads (Tyco/Kendall) Primapore® Coversite® (Smith & Nephew) Tenderwet® (Medline) Medipore® (3-M) Coverlet® (BSN-Jobst)	There are no published studies using this category on diabetic foot ulcers. In one clinical study (not published) with 302 patients Telfa with a placebo gel was used as the control arm. 30% healed in 12 weeks
Transparent films	Provide moist environment, transparent, waterproof, adhesive	Good for very superficial wounds that do not drain much, can cause maceration, if strike through occurs can allow bacteria in	OpSite® (Smith & Nephew) Tegaderm® (3-M) BlisterFilm® Polyskin® (Tyco/ Kendall) Suresite® (Medline)	There are no published studies available on diabetic foot ulcers. Up to 50% enhanced healing in superficial wounds when compared to air exposed wounds [26]
Foam dressings	Foamed polymer solutions, absorption generally depends on thickness, contact layer is nonadherent	Provides good absorption for partial thickness and moderately draining full thickness wounds, foams can be treated with agents to enhance absorption, most are coated with thin film that serves as a barrier	Allevyn® (Smith & Nephew) Biatain® (Coloplast) 3 M Foam (3-M) Curafoam® Hydrasorb® (Tyco/Kendall) Polymem® Polymax® (Ferris) Tielle® (J & J) Lyofoam® (Convatec) Optifoam® (Medline)	There are no published studies available for diabetic foot ulcers. In venous ulcers with 50 patients 34% in 13 weeks [67]. In pressure ulcers with 50 patients 20% of stage II–III healed in 6 weeks [72]. 42% of 24 Stage II–III healed in 12 weeks [70]

(continued)

Table 16.2 (continued)

Category	Characteristics	Advantages/ disadvantages	Product examples	Evidence/research support
Hydrocolloid dressings	Wafers composed of gelatin, pectin and CMC. Absorption is slower and generally depends on thickness. They are self-adhering, impervious to air and gases	Provides excellent seal from the outside environment. Moldable, contours well to heels, good for superficial and full thickness wounds with mild to moderate exudation, provides excellent autolytic debridement	Exuderm® XCell® (Medline) Comfeel® (Coloplast) DuoDerm® (Convatec) Tegasorb® (3-M) Nu-Derm® (J & J) RepliCare® (Smith & Nephew) Restore® (Hollister) Ultec® (Tyco/ Kendall)	80% of 36 diabetic and Hansen's disease patients healed in 10 weeks with a hydrocolloid dressing and total contact cast [73, 74]. 88% of 84 ulcers in 45 patients healed in 14 weeks [66]. Probability of infection (measured retrospectively) was 2.5% [68]. 55% of 164 patients with long standing venous ulcers healed in 12 weeks when used with graduated compression [69]. A biocellulose dressing XCell® was reported to be more effective ($p = 0.0094$) than standard care for autolytic debridement of venous ulcers [28]
Hydrogel sheets	Cross-linked hydrophilic polymers insoluble in water interact with exudates by swelling	Comformable, permeable, absorbancy is based on composition, must use a secondary dressing to anchor	Nu-Gel® (J &J) Curagel® Aquaflo® (Tyco/ Kendall) Derma-Gel® (Medline) Elasto-Gel® (Southwest) FlexiGel® (Smith-Nephew) CaraDres® (Carrington)	There are no published studies available on diabetic foot ulcers. In partial thickness and full thickness acute wounds hydrogels increase healing by 30–36% [15, 16, 26]
Amorphous hydrogels	Water, polymers and other ingredients combined into a topical that donates moisture, when combined with CMC can provide absorption as well	Helps to rehydrate and soften wound tissues. Good for superficial wounds, such as cracks due to dry skin	Curasol® (Tyco/ Kendall) IntraSite® SoloSite® (Smith-Nephew) Dermagran® (Derma Sciences) WounDress® (Coloplast) DuoDerm® Hydroactive (Convatec)	There are no published studies available in diabetic foot ulcers. In acute partial thickness wounds healing was accelerated by 28% compared to untreated [16, 26]
Alginates	Nonwoven pads and ropes of natural polysaccharide fibers derived from seaweed. On contact with wound fluid alginates gel	Indicated for wound with moderate to heavy exudates, they require a secondary dressing to anchor	AlgiSite® (Smith-Nephew) AlgiCell® (Derma Sciences) Maxorb (Medline) Kaltostat® (Convatec) SeaSorb® (Coloplast) Sorbsan® (Bertek)	There are no published studies available on diabetic foot ulcers. Favorable healing compared to standard care has been reported in pressure ulcers [75], venous ulcers [76], and dehisced wounds [77]

(continued)

Table 16.2 (continued)

Category	Characteristics	Advantages/ disadvantages	Product examples	Evidence/research support
Hydrofibers/ hydropolymers	Consist of foamed gels or highly absorbent fibers, wick exudates away from the wound	Useful for heavily draining ulcers or when extended use is desirable	Aquacel® (Convatec) Exu-Dry® Allevyn® Plus (Smith-Nephew) Tielle® Plus (J & J)	There are no published studies available on diabetic foot ulcers. In preclinical animal models, this dressing category speeds healing by approximately 30% compared to untreated [78]
Medicated/ antimicrobial dressings	Dressings that deliver the effects of agents, such as cadexomer iodine, silver and PHMB	Useful when localized minor wound infection is present and to lower bacterial bio-burden, some provide odor control	Acticoat® (Smith-Nephew) Contreet® Ag foam, hydrocolloid (Coloplast) Actisorb® Silvercel® (J & J) Aquacel® Ag (Convatec) Arglaes® SilvaSorb® XCell® AM Maxorb® Ag (Medline) Silverlon® (Argentum) Telfa® AMD (Tyco/Kendall) Iodosorb® Iodoflex® (Healthpoint)	Cadexomer iodine was shown to improve the healing of foot ulcers in diabetic patients [32] In venous ulcers, Iodosorb significantly improved wound closure in a 12-week study with standard compression [31] Acticoat® effective in lowering bacterial counts in burns [72]. There are many in vitro studies reporting bacterial kill when using silver or PHMB
Combination/ impregnated dressings	Gauzes and nonwovens saturated with an agent or compound	Good for providing a nonadherent surface to the wound, some dressings may deliver zinc salts, mild antibacterial agents, or a moist soothing occlusive, such as petrolatum	Adaptic® (J & J) Aquaphor® (Smith-Nephew) Curasalt® Xeroform® Xeroflo® (Tyco/ Kendall) EpiMax® (Dermagenics) Mesalt® (Molnlycke)	There are no published studies available on diabetic foot ulcers. Impregnated gauze has been reported to only slightly enhance healing (5%) compared to air exposure in superficial wounds [26]
Collagens and dermal matrix materials	Gel pads, particles, pastes, powder, sheets derived from human, porcine, bovine or avian collagen. Some are combined with oxidized cellulose, silver or alginate	These dressings should be used in clean wounds. The collagen bioerodes and may provide a temporary provisional matrix to protect the wound from harmful proteases	Promogran® Prisma® Fibracol® (J & J) Biobrane® (Bertek) Oasis® (Healthpoint) Stimulen® (Southwest) Primatrix® (TEI Biosciences) GrafJacket®, AlloDerm® (Life Sciences) Integra® (Integra Life Sciences)	45% of the 95 patients treated with Promogran® healed compared to 33% of 89 treated with moist gauze [79]. Statistical significance was not reached ($p = 0.056$) in this trial. 49% of 37 diabetic foot ulcer patients treated with small intestine submucosa (SIS Oasis®) healed in 12 weeks compared to 28% treated with beclapermin (the difference was not statistically significant [80]). Preliminary results of a randomized controlled trial show faster healing with acellular human dermal matrix (GraftJacket®) versus moist gauze [81]

(continued)

Table 16.2 (continued)

Category	Characteristics	Advantages/ disadvantages	Product examples	Evidence/research support
Skin equivalents and tissue engineered skin products cell therapy	Living human skin cells incorporated in a matrix usually consisting of collagen. This cell therapy provides growth factors and cytokines to the wounds	Only Apligraf® and Dermagraf® are approved by FDA for the treatment of diabetic foot ulcers. Most beneficial when the wound bed is healthy without the presence of nonviable tissue	Appligraf® (Organogenesis) Dermagraft® Transcyte® (Smith-Nephew) OrCel® (Ortec) Epicel® (Genzyme)	In a diabetic foot ulcer study of 208 patients, 75% healed in the group treated with Apligraf® compared to 41% in the control group ($p<0.05$). In the same study the time to healing in the Apligraf® group was 38.5 days compared to 91 days for the control group [82]. Diabetic foot ulcer patients treated with Dermagraft® had a statistically significant higher percent wound closure by week 12 than patients treated with moist gauze [57]. The percentage of patients who experienced wound infection was less in the Dermagraft® treatment group

adhesive border are useful for very superficial minimally draining wounds. Be sure that the adhesive is safe for use with diabetic skin and does not reinjure upon removal.

Transparent film dressings were first introduced as IV site dressings or surgical incise drapes. They were used as wound dressings in the late 1970s and have been shown to promote the healing of partial thickness minimally draining wounds [20]. We find that transparent film dressings are not useful for the treatment of diabetic foot ulcers mainly because they do not have any absorptive capacity. The exudates tend to remain in contact with the wound and surrounding skin causing maceration. In addition, frequent strike-through eliminates the edge seal and exogenous bacteria can gain entry. For superficial abrasions, skin tears, and diabetic bullae, transparent films are useful when used together with a topical antibiotic agent.

Foam dressings combine occlusion and moist wound healing with some degree of absorption. These wound dressings are made from foamed urethane or another polymer creating open compartments (open cell foam) that house the exudates. To a certain degree, absorption by a foam dressing depends on the size and number of open cells generated during the foaming process. Most foam dressings are between 0.5 and 1 cm thick. Foams have a thin urethane film covering the outer surface. This polymeric film over the top maintains the moist environment by regulating the moisture vapor transmission rate (MVTR). The film covering also provides a seal to water and exogenous bacteria. Foam dressings may have an adhesive coating over the wound contact layer or may have an island configuration where the foam is at the center and the perimeter provides the adhesive contact layer. Foam dressings may also contain additives, such as surfactants, glycerin, or superabsorbents aimed at improving the function of the foam. There are also foam dressings that are impregnated with antibacterial agents, such as silver or polyhexamethylene biguanide (PHMB). Foam dressings are appropriate for diabetic ulcers with moderate to heavy drainage, or for ulcers with minimal drainage where the dressing can remain in place for 3–7 days. Unless the foam is an island dressing where adhesive covers the perimeter, a secondary dressing, adhesive tape or a bandage will be necessary to anchor the product. The foam design will imbibe wound fluid and keep it away from the wound. For chronic wounds (or wounds that are >2 months old), this is a desirable attribute as it has been shown that chronic wound

fluid may be harmful to cells and provisional matrix [21]. Foam dressings also provide a cushion that may be helpful to protect the wound from friction or trauma.

Hydrocolloid dressings are the direct descendants of ostomy devices and barrier products. Hydrocolloid dressings are completely air-tight and do not allow the transport of oxygen or other gases. In the 1970s, wound healing research with hydrocolloids dispelled the old notion that "the wound should be allowed to breathe" [22]. From these studies, it became obvious that the oxygen necessary for wound repair came from the blood and that atmospheric oxygen often harmed or delayed the healing process [23]. These dressings are created by mixing a hydrocolloid, such as carboxymethyl cellulose (CMC) with gelling agents, such as gelatin, and combining them with an adhesive elastomer, such as isobutylene. Hydrocolloids are dispersions of discrete particles around which water molecules and solvated ions form a shell-like structure. Fluid absorption occurs principally by particle swelling and enlargement of this structure. The hydrocolloid mass of these dressings consists of gum-like materials, such as guar or karaya, sodium CMC, and pectin, bound by an adhesive such as polyisobutylene. Certain hydrocolloid formulations can adhere to wet surfaces (wet-tack) because of particle swelling and phase inversion. When placed over a moist wound the immediate wound contact area dissolves in time to form a semisolid gel that allows for dressing removal without reinjury. Exudate absorption by most hydrocolloid dressings results in the formation of a yellow/light brown gelatinous mass that remains covering the wound upon dressing removal. This may be irrigated from the wound and should not be confused with pus. As hydrocolloids and gelatin decompose over the wound, there may be a characteristic odor that resolves once the wound has been cleansed. Hydrocolloid dressings are particularly useful when autolytic debridement is desirable [15, 23]. The wound environment created under a hydrocolloid dressing is acidic (pH 5) and has been shown to inhibit the growth of pathogens, such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* [24]. Although hydrocolloid dressings are absorbent, they do not absorb wound fluid at the same rate as traditional dressings (made with gauze or nonwoven), foams, biocellulose dressings, or alginates.

Hydrogel sheets are three-dimensional lattices made up of a hydrophilic polymer, such as polyvinylpyrollidone. Hydrogel dressings are nonadherent and have a high water content. Hydrogels allow a high rate of evaporation without compromising wound hydration. This property makes them useful for burn treatment or large superficial abrasions. Compared to untreated, hydrogel as well as hydrocolloid dressings have been reported to increase epidermal healing by approximately 40% [25]. Hydrogel dressings are soothing and have been shown to cool the skin by as much as 5°C [15, 26]. Hydrogel dressings are not very useful for diabetic (neuropathic) foot ulcers unless the wound is very shallow and only drains minimally. However, they are useful for excoriation or cracking caused by dry skin in this patient population. Hydrogel dressings are also useful to treat painful inflammatory ulcers and other superficial wounds caused by trauma.

Included in this category, though not true hydrogel sheets are biocellulose wound dressings. A biocellulose wound dressing made from purified bacterial cellulose that can both deliver or absorb moisture has been introduced. This dressing accelerates autolytic debridement while it provides a protective seal over the wound similar to a blister roof [27].

Amorphous hydrogels come packaged in tubes, spray bottles or foil packets, and they may also be impregnated into gauze. In the amorphous hydrogel, the hydrophilic polymer has not been cross-linked and therefore remains in a more aqueous (gel-like) state. The primary ingredient is water and can dry rather quickly if not covered with a semi-occlusive or occlusive dressing. Several amorphous hydrogels contain additives, such as

collagen, calcium alginate, or CMC, in order to be more absorptive. Like a moisturizing agent, amorphous hydrogels will donate moisture and can be useful to soften dry eschar or callous.

Alginate dressings are the calcium salts of alginic acid (derived from brown seaweed) that have been spun into a fiber. These dressings are available as compressed nonwoven sheets or bound into ropes. When wound fluid contacts the calcium alginate, the sodium in the fluid replaces the calcium in the alginate increasing the viscosity of the fluid producing a gel (sodium alginate). Alginates are emulsifiers and serve as thickening agents that are frequently used in prepared foods. Alginates are bioerodible and will gradually dissolve with moisture over time. The greatest advantage of the alginate dressings is their absorptive capacity. Alginates are ideal for heavily draining wounds. If used appropriately, they can significantly reduce the number of dressing changes required. If used in wounds that drain minimally, the fibers will dry out and will adhere to the wound bed. The secondary dressing is important and one should be chosen that helps to keep the gel moist. Alginates have been reported to have hemostatic and bacteriostatic properties [28]. Alginate dressings are also available with the topical antibacterial silver.

Hydrofibers are fibers of CMC. Hydrofiber dressings rapidly absorb exudates and have a large absorptive capacity (approximately two to three times greater than alginates) [29]. Obviously, they are indicated for heavily draining wounds or when extended wear is required. Hydrofibers can also contain silver with the intent to reduce the wound's bacterial burden. In patients with neuropathic ulcers that are being treated with a total contact cast the hydrofiber dressing can be kept on for 7 days. It has been our experience that the hydrofiber containing silver helps to reduces wound odor.

Hydropolymers are foamed gels that wicks exudates away from the wound to the upper layers of the pad. The backing material has a very high MVTR and allows for the evaporation of excess fluid. Hydropolymer dressings are available with silver as well. These dressings are useful for moderate and heavily draining wounds or when the dressing needs to remain in place for an extended period of time.

Medicated dressings are devices that contain an agent (usually an antimicrobial) in order to supplement its function. Recently, there has been great interest in the use of silver-containing dressings. The antimicrobial properties of metallic silver have been used empirically for thousands of years and a great deal has been published regarding its mechanism of action, toxicity, and historical background [25]. Many dressings have been introduced that contain silver in a variety of different forms. There are dressings that contain a silver-coated polyethylene membrane, ones that contain silver-impregnated activated charcoal cloth, alginates, foams and hydrocolloids containing silver, microcrystalline silver on the adhesive portion of a transparent film, silver powders, and even an amorphous hydrogel containing silver. The antimicrobial properties of several of these silver-containing dressings have been studied previously [30]. Interestingly, the silver content and antimicrobial activity of the various dressings varies considerably. PHMB has been used as an antimicrobial agent by the contact lens industry for years. Recently, several manufacturers have incorporated this antimicrobial agent into their wound dressings. A biocellulose wound dressing containing PHMB has recently been introduced and PHMB has also been impregnated into gauze and nonwoven.

Iodine preparations have been criticized in the past because of their cytotoxicity. However, in cadexomer iodine formulations the iodine is released in quantities that are not harmful to cells. Cadexomer iodine is available in an absorbent gel and also as a paste dressing. Cadexomer iodine has been studied in both venous ulcers [31] and diabetic foot ulcers [32] with favorable results, but these studies had relatively small sample populations. A randomized controlled clinical trial of cadexomer iodine for the treatment of diabetic foot ulcers has not been done to date.

Combination products/impregnated gauze dressings are gauzes and nonwovens that are incorporated with agents that affect their function. Dressings have long been used as drug delivery devices. Agents most commonly used include saline, oil, zinc salts, or petrolatum, Vaseline®, Aquaphor®, or (bismuthtribromophenate) bacteriostatic agents. Gauze or polyethylene may also be impregnated with salts and inorganic ions that are appear to decrease the harmful effects of matrix metalloproteases (MMPs) in chronic wounds.

Silver dressings have been used for its antimicrobial properties for thousands of years, and were formally accepted by the US Food and Drug Administration for wound management in the 1920s. There are many different types of silver wound dressings, including films, alginates, foams, hydrogels, and hydrocolloids. While the exact mechanism of action of silver-based products is unknown, silver colloid is active against both *Methacillin Resistant Staph Aureus (MRSA) and Pseudomonas aeurginosa* [33].

Though the use of silver-based wound dressings is now prolific, the evidence of its efficacy is still unknown. A recent systemic review of 26 randomized controlled trials did not find evidence of increased wound healing on uninfected wounds with silver [34]. More specific to diabetic wounds, a systematic review examining the efficacy of silver in healing diabetic foot ulcers did not find any studies that met the inclusion criteria—a randomized control trial with diabetic ulcers comparing silver dressings to a control—and concluded that more trials are needed to determine effectiveness [35]. More studies are needed to determine the efficacy of silver on diabetic foot ulcerations.

Honey, a sugar solution modified by a honeybee from nectar, has been used to promote wound healing since ancient times. Due to its acidic pH, low water content, and hydrogen peroxide secretions, honey is less likely to develop resistance against organisms in a wound [36]. Mostly used medicinally in tube or gel form, honey is applied either to gauze or directly to the wound and changed daily. As the wound secretions lessen, the number of required dressing changes decreases.

A controlled, comparative study between honey and povidone iodine for Wagner type II diabetic ulcerations in 30 patients did not find statistical significance between the two groups in healing time [37]. A recent systemic review found insufficient evidence for the use of honey in clinical practice for chronic, diabetic wounds [38]. More research is needed to accurately determine the effectiveness of honey on wound healing.

Growth Factor Therapy

Growth factor therapy is a promising approach to wound healing addressing the deficiency of growth factors common to the chronic wound. As more knowledge about wound environments is understood, the focus of future wound therapy treatments has turned to growth factors and stem cells. Currently, the only platelet-derived growth factor gel approved by the FDA for diabetic ulcerations is Becaplermin (rhPDGF-BB). Initial evaluation of rhPDGF-BB effectiveness on chronic wounds was performed in decubitus ulcers [39, 40]. In both studies, ulcers treated with the higher dose of rhPDGF-BB demonstrated increased wound closure rates and greater reduction of wound volume. However, complete wound closure was not a primary endpoint in either study, raising questions as to the ability of rhPDGF-BB to effect wound closure.

As a result of the early promising data from decubitus ulcers, a prospective, randomized, double-blinded study of rhPDGF-BB was performed on diabetic neuropathic foot ulcers [41]. Patients were treated with rhPDGF-BB at a dose of 2.2 μg/cm^2, CMC, or vehicle alone for 20 weeks or until complete wound closure occurred. Results from this study demonstrated that 48% healed following treatment with rhPDGF-BB while only 25% healed with vehicle alone ($p < 0.01$). The median reduction in wound area was 98.8% for rhPDGF-BB treated patients but only 82.1% for those treated with vehicle.

There were no significant differences in the incidence or severity of adverse events in either group. This was the first clinical trial to suggest that a growth factor, rhPDGF-BB, could be applied topically and be effective and safe in accelerating the healing of chronic wounds in humans. Despite its promise, it should be noted that judicious use of Becaplermin should be performed in concomitant malignancy as a recent black box warning was issued by the FDA as a result of evidence of increased mortality from malignancy when using three or more tubes [42].

In light of the success with rhPDGF-BB, investigation into the use of other growth factors, such as transforming growth factor (TGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and fibroblast growth factor (FGF) on diabetic neuropathic ulcers has been investigated. However, clinical studies examining the use of these growth factors have been conflicting, with some studies showing promise, while others have demonstrated little to no improvement of wound healing compared to control arms [43, 44]. As a result, there are no commercially available products using these growth factors on diabetic foot ulcers to date.

Antiseptic Wound Cleansers

Antiseptics are agents that kill or inhibit microorganisms on living tissue. Providone-iodine, 70% alcohol and hydrogen peroxide are still very commonly used today by both the public and health professionals. However, all three agents have been found to have only limited value in wound care today. Seventy percent isopropyl alcohol only shows limited effect against microorganisms and for only short amounts of time. It can be a strong irritant to an open wound and draws away moisture from the wound as it evaporates [45]. Povidone-iodine is very widely used in wound care. It is, however, not recommended for use in open wounds. Studies have shown that in vitro povidone-iodine, unless highly diluted is toxic to most cell types implicated in the healing process [46]. Because povidone-iodine is water soluble, diluting it actually releases free iodine into the tissue [47]. In certain patients where the primary goal is not wound closure (palliative wound care), povidone-iodine can be very effective at drying the eschar thus inhibiting the development of wet gangrene. Hydrogen peroxide 3% solution is also commonly used today. It cleanses the wound through its release of oxygen. It has been shown to delay wound healing by 8% compared to untreated [15, 26]. However, in patients who require at home wound care and hygiene is a concern it may be worthwhile to give in to the slight delay and use 3% hydrogen peroxide to cleanse the wound prior to dressing application. If hydrogen peroxide is diluted to 0.3%, its effectiveness against microorganisms is reduced [48–50].

Negative Pressure Wound Therapy

Negative pressure wound therapy (NPWT) consists of a sterile foam cell dressing that is applied directly over a wound and sealed from above with an adhesive film. An evacuation tube is placed into the foam, which is attached to a pump. The pumping action creates subatmospheric or negative pressure uniformly to all tissues within the wound [51] causing a gentle compression over the wound surface. The pressure may be intermittent or continuous, depending on NPWT has been credited with maintaining a moist wound environment, removing waste products, reducing edema, and stimulating the formation of granulation tissue [52].

A number of studies have compared the use of NPWT to standard wound care. In a multicenter, randomized-controlled trial with 342 patients, Blume et al. compared NPWT to wounds treated with alginate or hydrogel dressings. The authors found higher wound closure in ulcers randomized to NPWT treatment and concluded that NPWT is a safe and effective modality for improving the healing potential of diabetic foot ulcers [52]. However, several limitations including high dropout rate (only 68% of patients

completed the study), non-blinding, and failure to standardize ancillary care, such as use of antibiotics, appropriate pressure off-loading, and intermittent versus continuous pressure used with NPWT provided more variables that could have altered the outcome.

NPWT has also been used following partial foot amputations with reported success [53]. In this randomized, multicenter study, 162 patients with foot wounds following partial foot amputations to the metatarsal region were treated with NPWT or standard moist wound dressings [53]. The authors reported NPWT-treated wounds healed more frequently, healed at a faster rate, and formed granulation tissue at a more rapid pace compared to the standard wound care group. They concluded that NPWT treatment was a safe and effective method for accelerating the rate of wound closure and had the potential to reduce reamputation rates. While this report demonstrated the promise of NPWT-treated wounds following partial foot amputations, the rate of wound closure was only improved in the NPWT group only when surgical wound closure was included in the analysis. The decision for surgical wound closure was not clearly defined or described in the study, potentially limiting the support for the effectiveness of the NPWT as a stand-alone treatment.

As with all new modalities, the cost of NPWT is of critical importance in determining its role. Based on the data from the previous study, Apelqvist et al. performed a cost analysis based on length of hospital stay, procedures performed, and number of dressings changed on the 162 patients [54]. The authors concluded that a savings of $12,800 was realized when NPWT was used as a result of diminished resource utilization, such as fewer physician visits and wound care dressings needed. Furthermore, the patients treated with NPWT experienced higher rates of wound healing, also impacting the length of care needed.

While the role of NPWT in the care of diabetic foot ulcers remains a source of considerable debate, most systematic reviews and consensus statements have supported its ability to improve and increase the healing process [55]. However, guidelines have been proposed for the appropriate use of NPWT based on best available clinical evidence. NWPT is contraindicated in the presence of ischemia, active cellulitis, or osteomyelitis. In addition, good wound care, including periodic, aggressive debridement, pressure off-loading, as well as concomitant use of active wound care dressings, such as acellular matrix scaffolds was encouraged in combination with NPWT.

Low-Frequency Ultrasound

Low-frequency (40 kHz), low-intensity (0.1–0.8 W/cm^2) ultrasound is a novel debridement technique recommended for wounds that cannot tolerate sharp debridement as in the case of a sensate limb or an ischemic ulcer. To date, there is limited clinical trial evidence regarding this specific modality for debridement of diabetic foot ulcers. The most convincing evidence comes from a prospective, multicenter, double-blinded, sham controlled study of 63 patients with chronic diabetic foot ulcers [56]. The authors demonstrated that ulcers treated with the active 40 kHz ultrasound had a greater proportion of wounds healed compared to sham treatment (40.7% vs. 14.3%, $p=0.0366$) after 12 weeks of care. In addition to improved healing rates, the ultrasound treated group demonstrated diminished exudate by week 5 compared to the sham treated group, leading the authors to suggest that this modality may also decrease the wound bacterial bioburden.

In spite of the positive outcome, it was also noted that 5 of the 23 centers had not followed the treatment protocol properly, resulting in those ulcers not considered in the evaluation process. Thus, it was felt that further study of this debridement method was warranted. Furthermore, future studies with proper assessment of quantitative tissue culture at enrollment may more accurately assess the impact of low-frequency ultrasound on the bacterial bioburden.

The use of low-frequency ultrasound debridement has also been been prospectively studied in

ischemic ulcers. In a randomized, controlled trial of 70 lower extremity ulcers complicated by critical limb ischemia, 35 ulcers were treated with low-frequency ultrasound while the remaining 35 treated with standard wound care [57]. After 12 weeks, 63% of the low-frequency ultrasound group achieved greater than 50% of healing compared to only 23% of the standard care group. However, it was also noted that baseline $TcPO_2$ levels were most predictive of wound healing as opposed to treatment group, with those wounds demonstrating greater than 20 mmHg most likely to heal. Thus, the effectiveness of low-frequency ultrasound remains questionable based on currently available published studies.

Electrical Stimulation

Electric current has been shown to facilitate fracture healing, enhance fibroblast and epidermal migration, and provide antibacterial effects [58, 59]. One randomized controlled double blind clinical trial of 40 patients studied the effectiveness of high-volt (50 V with 80 twin peak monophasic pulses), pulse galvanic electric stimulation on diabetic foot ulcer healing [60, 61]. Sixty-five percent of the patients healed in the group treated with electric stimulation, whereas 35% healed with placebo ($p = 0.058$) While this study demonstrated positive wound benefits with electrical stimulation, the body of evidence consists primarily of small randomized studies or studies that used this technology in an off-label fashion. As a result, electrical stimulation has not been adopted as a routine treatment for chronic diabetic foot wounds.

When to Perform a Wound Culture

Routine culturing of wounds is not indicated. Wound cultures should only be taken when the wound has the clinical signs of infection or those that have no clinical signs of infection but are deteriorating or have failed to heal. For those wounds that have the clinical signs of infection swab cultures can provide useful data regarding the presence of potential pathogens and the diversity of microorganisms present as well as antimicrobial sensitivity. A swab sample can also provide a semiquantitative estimation of the microbial load (>105 CFU/ml). A correlation between semiquantitative swab data and quantitative biopsy data has previously been demonstrated [62, 63]. For deteriorating wounds or wounds failing to improve, a tissue biopsy culture for quantitative and qualitative analysis should be obtained.

Conclusions

Local care for diabetic foot ulcers should commence with a complete history and physical examination. Diagnostic procedures should be aimed at exclusion of osteomyelitis, dysvascular problems, extent of neuropathy, electrolyte imbalance, high or low blood glucose levels, nutritional defects and the use of agents that impede wound healing, such as corticosteroids, chemotherapeutic agents, and topical cytotoxic agents. Oral antibiotics should be prescribed if a wound infection is present. Topical antibiotics are helpful for localized minor infections combined with frequent examination until resolution. An ulcer care strategy combining moist wound care and effective off-loading should be developed for each patient. The patient should be followed and wounds measured regularly for 4 weeks. If (after 4 weeks) the wound has healed by 50% or more continue with the same treatments until healing. If the wound has not healed by 50% in 4 weeks, then an alternative (more aggressive approach) such as an active modality should be considered. A list of agents that have been studied in randomized clinical trials for the treatment of diabetic foot ulcers is presented in Table 16.3.

Table 16.3 Diabetic foot ulcer treatments that have been studied in randomized clinical trials

Treatments	Description/significance	References
Bilayered skin construct (Apligraf®)	75% healed in the group treated with Apligraf® compared to 41% in the control group ($p<0.05$)	[60]
Dermal construct (Dermagraft®)	Patients treated with Dermagraft® had a statistically significant ($p<0.05$) higher percent wound closure by week 12 than patients treated with control	[19, 61]
PDGF-BB Beclapermin (Regranex®)	Beclapermin (100 μg/g) combined with aggressive surgical debridement was effective in improving diabetic foot ulcer healing ($p=0.007$)	[63, 64]
Collagen-ORC wound dressing (Promogran®), Small intestine submucosa (SIS, Oasis® Wound Matrix)	45% of 95 patients treated with Promogran® healed compared to 33% of 89 treated with moist gauze. Statistical significance was not reached ($p=0.056$) in this trial. In a 73-patient diabetic foot ulcer trial, 49% of 37 in the Oasis® group healed after 12 weeks. Statistical significance was not reached ($p=0.055$)	[59, 76]
Hydrocolloid dressing (DuoDerm®)	80% of 36 diabetic and Hansen's disease patients healed in 10 weeks with a hydrocolloid dressing and total contact cast. 88% of 84 ulcers in 45 patients healed in 14 weeks	[66, 68]
Moist saline gauze	Moist-to-moist saline gauze has been considered standard care and therefore has been used as the control regimen in most clinical trials. Combined results show that 29–33% of ulcers treated with moist gauze heal within 12 weeks	[19, 59–61]

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Surgical Treatment of the Ulcerated Foot

17

John M. Giurini

Abstract

Foot ulceration with infection continues to be one of the leading causes of hospitalization for patients with diabetes mellitus. It has been previously reported that the incidence and prevalence of diabetic foot ulcerations is believed to be 15%. The rate of recidivism remains a staggering 50% with the majority of these ulcerations recurring within 18 months. This has significant economic ramifications on the health care system when one considers that the average total direct cost of healing an infected ulceration not requiring amputation is approximately $17,500 per episode.

Successfully treating diabetic foot infections and ulcerations requires a thorough understanding of the risk factors for ulcerations and amputations. It requires taking advantage of advances in antimicrobial therapy, wound healing strategies including topical growth factors, negative pressure wound therapy (NPWT), improved vascular interventions, and a more aggressive surgical approach where indicated. The key components for successful outcomes require the establishment of treatment algorithms utilizing the above advances and the identification of a dedicated team of health care professionals to manage these complex problems.

Keywords

Preoperative evaluation • Anesthesia techniques • Surgical approach • Forefoot procedures • First ray • Lesser digits • Lesser metatarsal procedures • Lesser metatarsal osteotomy • Lesser metatarsal head resection • Ulcer excision • Panmetatarsal head resection • Midfoot procedures • Ostectomy • Exostectomy • Fasciocutaneous flap • Medial column fusion • Hindfoot procedures • Calcanectomy • Tendo-Achilles lengthening • Midfoot arthrodesis • Triple arthrodesis • Pantalar arthrodesis

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Introduction

Diabetes continues to have a significant socioeconomic impact on the health care system of the United States. It was estimated that there were approximately 16 million people in 1997 with either diagnosed or undiagnosed diabetes mellitus in the United States [1]. Ten years later the CDC reports, there are nearly 24 million diabetic people or 7.8% of the population [2]. The incidence of diabetes does not appear that it will slow down any time soon. A recent study projects that by the year 2050 nearly 30% of the United States population will have diabetes [3].

As the incidence of diabetes rises, so will the cost of providing care rise to no one's surprise. In 1987, $20.4 billion was spent in direct and indirect costs of care for diabetic patients. In 1997, this had risen to $91.8 billion [1]. By 2007, the total cost for providing care to patients with diagnosed diabetes nearly doubled to $174 billion [2].

Foot ulceration with infection continues to be one of the leading causes of hospitalization for patients with diabetes mellitus. It has been previously reported that the incidence and prevalence of diabetic foot ulcerations is believed to be 15% [4]. The rate of recidivism remains a staggering 50% with the majority of these ulcerations recurring within 18 months. This has significant economic ramifications on the health care system when one considers that the average total direct costs of healing an infected ulceration not requiring amputation is approximately $17,500 per episode [5].

Diabetic patients remain 15 times more likely to undergo a major lower extremity amputation than nondiabetic patients with the total number of major limb amputations being around 71,000 [2]. In 1993, this number was around 50,000 [6]. The cost for lower extremity amputation ranges between $30,000 and $33,500 [5]. In 1993 this amount was $600 million [1, 4]. The Department of Health and Human Services had set a goal of a 40% reduction in the number of diabetic amputations by the year 2000 [7]. Needless to say, we have not met that goal.

Successfully treating diabetic foot infections and ulcerations requires a thorough understanding of the risk factors for ulcerations and amputations. It requires taking advantage of advances in antimicrobial therapy, wound healing strategies including topical growth factors, negative pressure wound therapy (NPWT), improved vascular interventions, and a more aggressive surgical approach where indicated. The key components for successful outcomes require the establishment of treatment algorithms utilizing the above advances and the identification of a dedicated team of health care professionals to manage these complex problems [8–11].

Goals of Surgery

The goals of surgery in patients with neuropathy differ from the goals of surgery in patients with normal sensation. It is important that these goals are clearly delineated and understood by both the patient and the surgeon.

The primary reason for surgical intervention in patients with normal sensation is to correct an underlying deformity and reduce or eliminate a patient's pain. In the absence of pain as in the neuropathic foot, the primary goal of surgery is to reduce the risk of lower extremity amputation by correcting a structural deformity which may lead to ulceration, or to eliminate a focus of osteomyelitis (Table 17.1).

Another important distinction to make is the difference between elective surgery, prophylactic surgery, and urgent surgery, as it relates to diabetic foot surgery. Elective surgery implies the presence of a deformity that can be corrected surgically but does not put the patient or the limb at immediate risk. Oftentimes, these deformities in the diabetic patient can be managed without surgery. There are clearly clinical situations where this type of conservative approach is in the patient's best interest.

Table 17.1 Surgical goals in the insensate patient

• Reduce risk for ulceration/amputation
• Reduce foot deformity
• Provide stable foot for ambulation
• Reduce pain
• Improve appearance of foot

Prophylactic surgery is surgery performed to prevent a more serious event. In the case of the diabetic patient with neuropathy, this event is most likely some type of imminent amputation. This implies the presence of a deformity and a history of a chronically recurrent ulceration that puts the limb at risk. The goals of surgery in this scenario are to eliminate the deformity, reduce the risk of reulceration, and reduce the risk of amputation.

Urgent surgery is self-explanatory. These patients commonly present with foul-smelling ulcerations with purulent drainage and cellulitis. Necrosis and abscess formation are not uncommon. These patients require immediate surgical intervention. The ultimate goal of surgery is to control the infection, to prevent the patient from becoming septic, and to save as much of the foot and/or leg as possible.

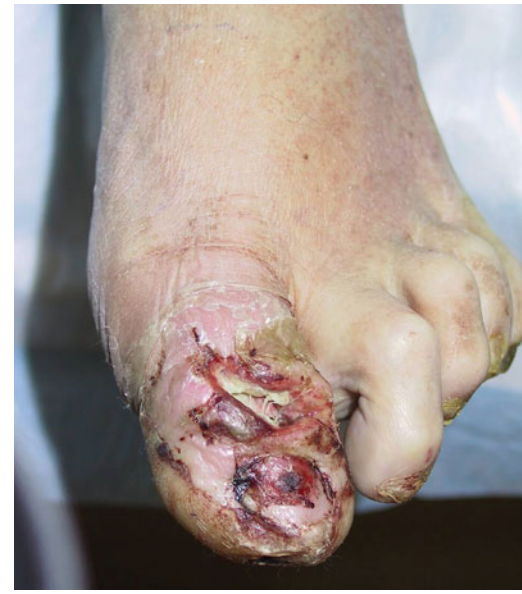

Fig. 17.1 Failure to recognize critical ischemia resulted in surgical failure in diabetic patient with autonomic neuropathy

Preoperative Evaluation

A detailed present and past medical history, past surgical history, list of current medications, and identification of risk factors such as smoking and nephropathy are critical to proper preoperative risk assessment. Patients with long-standing diabetes mellitus will often present with cardiac and renal complications which must be managed to reduce the morbidity and mortality of a local foot procedure [12]. The surgeon is well advised to obtain consultations with cardiology, nephrology, and endocrinology whenever appropriate.

The vascular evaluation of the diabetic foot requires special attention. Diabetic patients with strongly palpable pedal pulses will usually heal a local foot procedure without difficulty. Patients who have weakly palpable or nonpalpable pulses at the level of the dorsalis pedis or posterior tibial artery require further vascular evaluation in the form of pulse volume recordings or a formal vascular surgery consultation. Lower extremity revascularization is often necessary prior to limb-sparing foot surgery [13]. Patients with autonomic neuropathy however require special mention. These patients will often present with pink, warm skin on the surface of the foot. This can be easily mistaken for a foot with good arterial perfusion even in the presence of critical ischemia (Fig. 17.1).

It has become increasingly important in recent years to obtain a detailed social history. More of the burden for the patient's aftercare is being placed on the patient's family. The majority of patients will require daily dressing changes and prolonged periods of non-weight bearing. For this reason, visiting nurses, home health aides, and physical therapists have become vital members of the multidisciplinary team. In situations where there is less than adequate support for these services at home, admission to a rehabilitative center should be considered. These factors should be identified early in the course of the patient's hospitalization so that discharge planning can proceed in a timely and stress free manner.

Anesthesia Techniques

The presence of profound peripheral sensory neuropathy and the localized nature of many of these procedures make local anesthesia with monitored intravenous sedation ideal for diabetic

patients undergoing foot surgery. Epidural or general anesthesia should only be contemplated when more extensive surgery is being considered. This includes most major procedures of the hindfoot and ankle. It should be remembered that either of these techniques increases the perioperative morbidity and mortality. The final choice of anesthesia should be made following discussion with the anesthesiologist and the patient's primary medical doctor and with a clear understanding of the procedure being performed.

Surgical Approach

Prior to definitive surgery or correction of an underlying deformity, the foot must be free of any acute infection. This implies that any area of undrained sepsis has been adequately drained and all necrotic tissue debrided to healthy granular tissue. The proper technique for draining wounds is to incise the wound in such a fashion to promote dependent drainage. As the patient lies recumbent in bed with the extremity elevated, the wound drains from distal to proximal (Fig. 17.2) [14]. Multiple stab incisions with the use of Penrose drains should be avoided as they do not promote dependent drainage. Any tissue that appears infected or necrotic should be sharply excised at this time, including any exposed or infected bone. The wound is then packed widely open and inspected daily for the resolution of sepsis, cellulitis, and the development of healthy granulation tissue. The goal of this initial surgical debridement is to convert an acute infection into a chronic wound. While negative cultures following initial debridement are preferred, it is not a prerequisite for definitive surgery and wound closure as additional surgical debridement is performed at the time of wound closure.

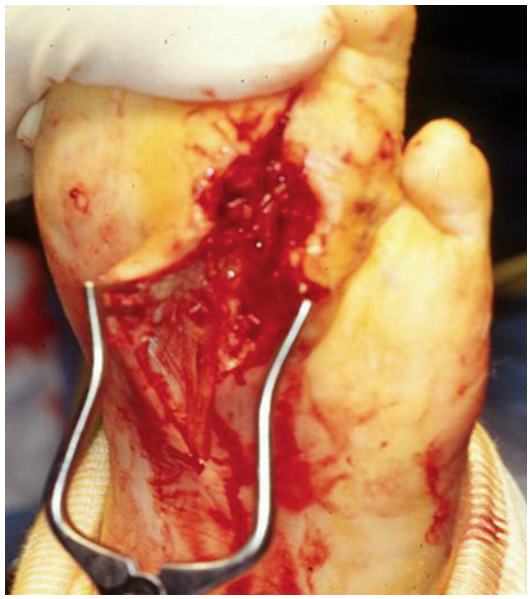

Fig. 17.2 An appropriate incision and drainage of infection should allow dependent drainage as the patient lies recumbent in bed

Forefoot Procedures

First Ray

While there are no studies showing the incidence of ulcers by location, ulcerations of the first ray (hallux and 1st metatarsal) are clearly among the most common ulcers treated. Common sites of ulcerations include the following: (1) plantarmedial aspect of the hallux, (2) distal tip of the hallux, (3) directly plantar to the interphalangeal joint of the hallux, (4) directly plantar to the metatarsophalangeal joint, (5) directly plantar to the first metatarsal head, (6) medial aspect of the first metatarsal head. The primary reason that this area is so susceptible is the combination of increased weight-bearing forces across this joint and faulty biomechanics which can lead to excessive pronation [15–17]. Excessive pronation leads to a medial transfer of the weight-bearing forces through the medial longitudinal arch, the first metatarsal, and ultimately the hallux [18].

Any structural deformity such as osteoarthritis, hallux limitus/rigidus, or severe plantarflexion will increase the susceptibility of this joint to ulceration by altering the biomechanics of the joint. Assessing the underlying structural or mechanical cause of the ulceration is vital to understanding the reasons for ulceration and for selecting the most appropriate procedure.

Ulcerations of the hallux, either plantarmedial or directly plantar to the interphalangeal joint, are most commonly related to abnormal biomechanics

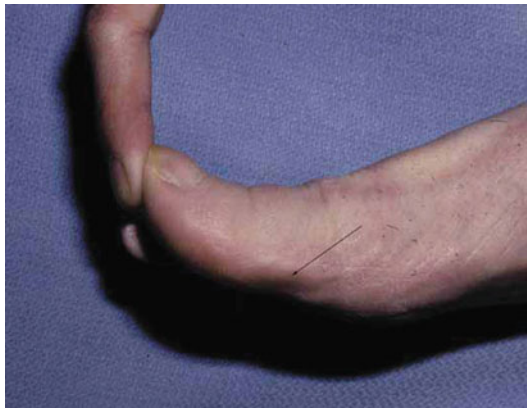

Fig. 17.3 A common location for ulcerations of the great toe is on the plantarmedial aspect of the interphalangeal joint of the hallux. The most common reason for these ulcerations is a hallux limitus

of the first ray resulting from excessive pronation. This is often manifested by the development of callus on the medial aspect of the hallux ("medial pinch" callus) or limitation of motion at the 1st metatarsophalangeal joint (i.e., hallux limitus) (Fig. 17.3). Hyperextension of the interphalangeal joint occurs to compensate for this lack of motion [19, 20]. Other less common causes of ulceration are an enlarged medial condyle on the distal phalanx or the presence of an interphalangeal sesamoid bone, in which case the ulceration is typically directly plantar to the interphalangeal joint.

The surgical treatment of this entity clearly depends on the underlying cause. When the cause of the ulceration is related to lack of adequate motion, restoring motion by way of an arthroplasty of the hallux interphalangeal joint (HIPJ) or of the 1st metatarsophalangeal joint (MTPJ) can be helpful. Resection of the head of the proximal phalanx relieves excessive plantar pressure and allows for resolution of the ulceration [21]. This procedure can also be employed when osteomyelitis of the head of the proximal phalanx is suspected. Occasionally, resection of an enlarged medial condyle can be effective in eliminating the callus. This, however, can result in instability of the joint and development of Charcot joint disease. In cases where there are significant degenerative changes at the level of the 1st MTPJ or complete lack of dorsiflexion, it is best to resect the base of the proximal phalanx and increase motion at this joint.

Surgical treatment of ulcerations directly plantar to the first metatarsal head can be addressed with excision of one or both sesamoid bones. During the propulsive phase of gait, the sesamoids migrate distally and plantarly, thus becoming more prominent. In the intrinsic minus foot, this could serve as a potential pressure point and site of ulceration.

The basic indication for sesamoidectomy is the presence of a chronically, recurrent ulceration directly plantar to the first metatarsal head without clinical or radiographic evidence of osteomyelitis of the 1st metatarsal head [22]. Contraindication for this procedure is the presence of significant degenerative changes of the 1st MTPJ or osteomyelitis of the 1st MTPJ. These are best treated with a Keller or 1st MPTJ arthroplasty. Additionally, the presence of a rigid plantarflexed 1st ray may be a relative contraindication to sesamoidectomy.

When the ulceration is found to extend to the level of the joint, osteomyelitis should be clinically suspected. Treatment must involve complete resection of the infected bone and joint. The procedure of choice is resection of the first MTPJ with excision of the ulceration. Although there may be alternate methods for addressing this problem surgically, there are clear advantages to utilizing this approach rather than allowing the ulcer to heal by secondary intention. By excising the ulceration, all infected, nonviable tissue is removed. It also allows for excellent exposure of all potentially infected tissues, such as the flexor hallucis longus tendon and the sesamoids which are commonly involved. Wounds which are closed primarily heal more predictably and with less scarring. As a rule, these wounds heal in 3–4 weeks. The healing rate of wounds which are allowed to heal by secondary intention is dependent on size and depth. The longer these wounds remain open, the greater the risk of secondary infection, as patient compliance often becomes an issue. While disadvantages exist to closing these wounds primarily, it is our philosophy that the benefits of primary closure outweigh the risks.

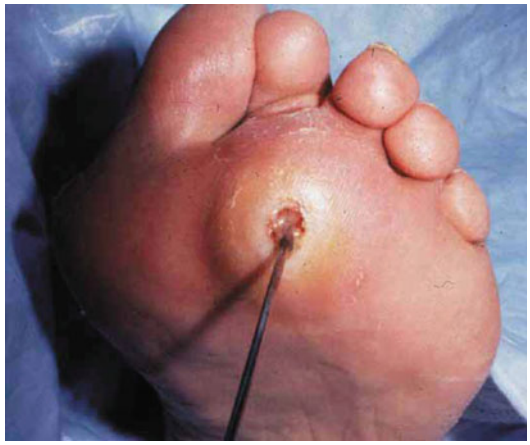

Fig. 17.4 The presence of synovial drainage from an ulceration is indicative of joint involvement and requires resection of that joint

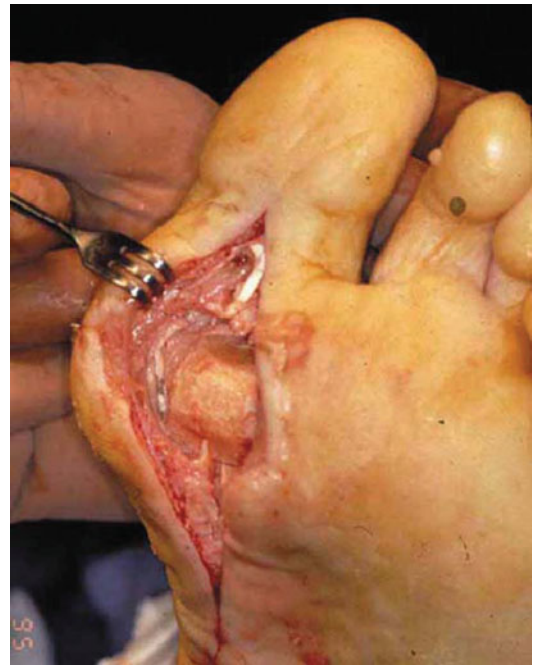

Fig. 17.5 Osteomyelitis of the 1st metatarsophalangeal joint is best addressed by elliptical excision of the ulcer with resection of the joint. Adequate resection of the 1st metatarsal should be performed to assure complete eradication of infected bone

The indication for first MTPJ resection with ulcer excision is the presence of an ulcer directly plantar to the first MPJ with direct extension into the joint. This is best determined by the ability to pass a blunt sterile probe through the ulceration and palpate bone. Additionally, the presence of clear, viscous drainage is indicative of synovial fluid. This is an ominous sign, as this can only come from the joint itself (suggesting a tear in the joint capsule) or from the sheath of the flexor hallucis longus tendon (Fig. 17.4). Even in the presence of negative X-rays, this finding is sufficient to make a clinical diagnosis of osteomyelitis [23].

An elliptical incision is made which completely excises the ulceration. It is recommended that the ratio of incision length to width is at least 3:1. This allows the wound to be closed with as little tension as possible. This incision is full-thickness and is carried down to the first metatarsal joint (Fig. 17.5). This should excise all necrotic, infected tissue. At this point, the flexor hallucis longus tendon will be visible. Typically, focal necrosis within the body of the tendon is visualized, indicating infectious involvement. It is therefore best to sacrifice the tendon in order to prevent recurrence of the infection. Removal of the long flexor tendon will often require performing a lengthening procedure of the long extensor tendon on the dorsum of the foot. Failure to perform this could result in an extensus deformity of the great toe, making shoe fit difficult.

Once the tendon is removed, the sesamoids will be visualized. These should also be sacrificed as these are intra-articular structures and are in direct communication with the first MTPJ. The base of the proximal phalanx and the cartilage of the 1st metatarsal head are now resected. While it is preferred to leave as much of the first metatarsal behind as possible to maintain function, enough metatarsal head must be resected so as to remove all focus of osteomyelitis.

The wound is closed by using full thickness nonabsorbable sutures. 2-0 and 3-0 polypropylene (Prolene®) is generally a good choice, as it is nonabsorbable and monofilament. Sutures should be placed evenly and used to coapt skin edges with as little tension as possible. Deep sutures are generally avoided since they can serve as a potential focus of infection and may be difficult to retrieve at a later date if necessary. It is advisable to pack the proximal 1.0 cm of the wound with a

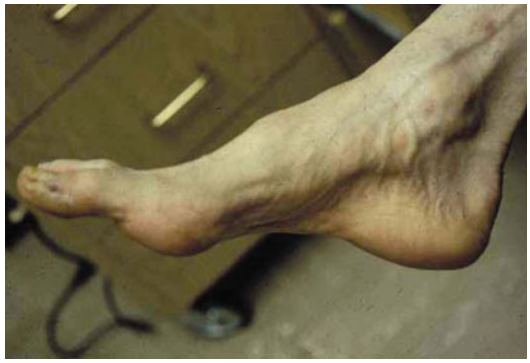

Fig. 17.6 Motor neuropathy is characterized by wasting of the instrinsic musculature in the arch of the foot. This typically results in deformities such as hammertoes, claw toes, or plantarflexed metatarsals

2×2 gauze sponge to promote drainage and avoid the development of a hematoma. This is usually removed after 24–48 h. This portion of the wound is then allowed to heal by secondary intention. The postoperative care mandates a period of total non-weight bearing of at least 4 weeks. Early ambulation will result in wound dehiscence, persistent drainage, postoperative infection and possible hypertrophic scar. The sutures are left in place this entire time.

Lesser Digits

Atrophy of the intrinsic muscles of the foot commonly occurs with the development of motor neuropathy. This can result in forefoot deformities such as hammertoes and claw toes (Fig. 17.6) [24]. When sensory neuropathy is also present, ulcerations develop over the proximal interphalangeal joint, at the distal tip of a toe or on adjacent sides of toes. Amputation of a lesser toe rarely results in long-term complications with the exception of loss of the second toe. This can precipitate a hallux valgus deformity. When ulceration is discovered early enough and treated aggressively, amputation of a toe can be avoided, thus maintaining function as well as appearance.

Hammertoes are either classified as reducible or nonreducible. A reducible hammertoe implies the deformity is being held by contractures of the soft tissues while a nonreducible deformity suggests there has been bone and joint adaptation as well as extensive soft tissue contractures. A reducible deformity is often amenable to correction by a tenotomy of the corresponding flexor tendon. A #61 Beaver blade is used to make a small stab incision just proximal to the flexor crease of the affected toe. It is then advanced until the flexor tendon can be palpated. The blade is used to transect the flexor tendon in a transverse direction. The tenotomy is facilitated by applying a gentle dorsiflexory force on the toe. This will put the flexor tendon under tension making it easier to palpate. Upon release of the tendon, the digital deformity can be felt to relax.

A nonreducible deformity requires resection of the phalangeal head as well as a release of the soft tissue. A proximal interphalangeal joint arthroplasty can be combined with excision of the ulcer. In long-standing hammertoe deformities, there may be a concomitant contracture at the level of the metatarsophalangeal joint, often indicative of a subluxation or even a dislocation. When dislocated, an area of high focal pressure can develop on the ball of the foot under the corresponding metatarsal head. This is often manifested as callus or even ulceration. Failure to recognize this fact can lead to incomplete correction of the deformity and failure to resolve the ulceration. The contracture at the metatarsophalangeal joint often requires a tenotomy and capsulotomy of the joint. If the joint cannot be relocated following release of the soft tissue alone, a shortening osteotomy of the metatarsal may be necessary to relocate the joint and relieve the plantar pressure.

Osteomyelitis of the tip of the distal phalanx can often be treated by local excision of the distal phalangeal tuft and primary closure of the ulceration. If, however, there is any concern of residual infection the wound may be left open and closed on a later date.

Lesser Metatarsal Procedures

The area under the lesser metatarsal heads represents the next most common location of diabetic foot ulcerations. Common causes of high foot pressures include abnormal foot mechanics, plantarflexed metatarsals, limited joint mobility, and prior surgical intervention [25–27]. While there are no definitive studies on ulcer incidence and

location, it appears that the second metatarsal is more susceptible to ulceration. This is most likely due to the second metatarsal's dependence on the mechanics of the first ray. When excessive pronation of the medial column occurs, there is increased weight transfer and pressure to the lateral metatarsals. This is most often manifested by the development of callus under the 2nd metatarsal head. After the 2nd metatarsal, the typical order of ulcer development is the 3rd metatarsal then the 5th followed by the 4th.

Selection of surgical procedures for ulcerations under the metatarsal heads requires careful evaluation of the ulcer. A critical determinant in the surgical management of these ulcerations is whether osteomyelitis is present.

Lesser Metatarsal Osteotomy

The primary goal of procedures to surgically treat metatarsal head ulcerations is to alleviate areas of high focal pressure. A metatarsal osteotomy can serve as a valuable adjunct in the management and resolution of these ulcerations [28]. The primary indication is the presence of a chronically recurrent ulceration under a metatarsal head without direct extension into bone. An incision is made dorsally over the involved metatarsal. Once the surgical neck is identified, a through and through osteotomy is made. A variety of techniques have been described for this osteotomy. We prefer either the V-type osteotomy with the apex directed toward the joint or the Weil osteotomy with screw fixation. The dorsal to plantar V-osteotomy provides a stable bone cut resistant to medial or lateral dislocation (Fig. 17.7). A small collar of bone can be resected allowing for both shortening and elevation of the metatarsal. This is often desirable when the metatarsophalangeal joint is either subluxed or dislocated. The metatarsal head is then elevated to the same level of the adjacent metatarsals. Fixation of the osteotomy with a .045 Kirschner wire is recommended. However, in the presence of an open ulceration, this is contraindicated. Fixation and stability is achieved by impacting the head onto the shaft. The patient is then maintained non-weight bearing for 4–6 weeks to allow for early bone healing.

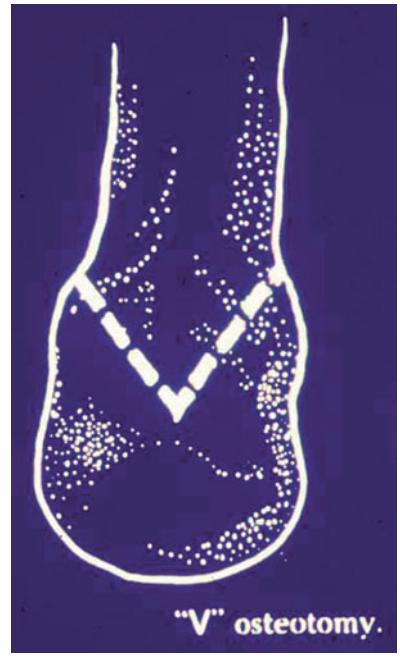

Fig. 17.7 A dorsal to plantar V-osteotomy through the surgical neck of the lesser metatarsal allows for adequate relief of plantar pressure overlying an ulceration. The medial and lateral wings of the "V" decrease the risk of medial or lateral dislocation of the metatarsal head

The Weil osteotomy can also be performed in this clinical situation [29]. In this approach, a 45° osteotomy is created in a dorsal-distal to plantar-proximal direction at the level of the surgical neck. It is then fixated with a single 2.0 cortical screw (Fig. 17.8). The advantage of the Weil osteotomy is that it shortens the metatarsal with little risk of dorsal dislocation. The Weil osteotomy works well in patients with a relatively normal to flatfoot. However, in patients with a rigid anterior cavus foot, the amount of proximal translocation is often not enough to resolve the ulceration. The V-osteotomy is the preferred procedure in this group of patients.

Complications following metatarsal osteotomies include transfer calluses or ulcerations and stress fractures of adjacent metatarsals. These most commonly result when the metatarsal head is elevated above the plane of the adjacent metatarsals. The risk of transfer problems can be reduced if the patient is fitted with an accommodative custom orthosis postoperatively. This will

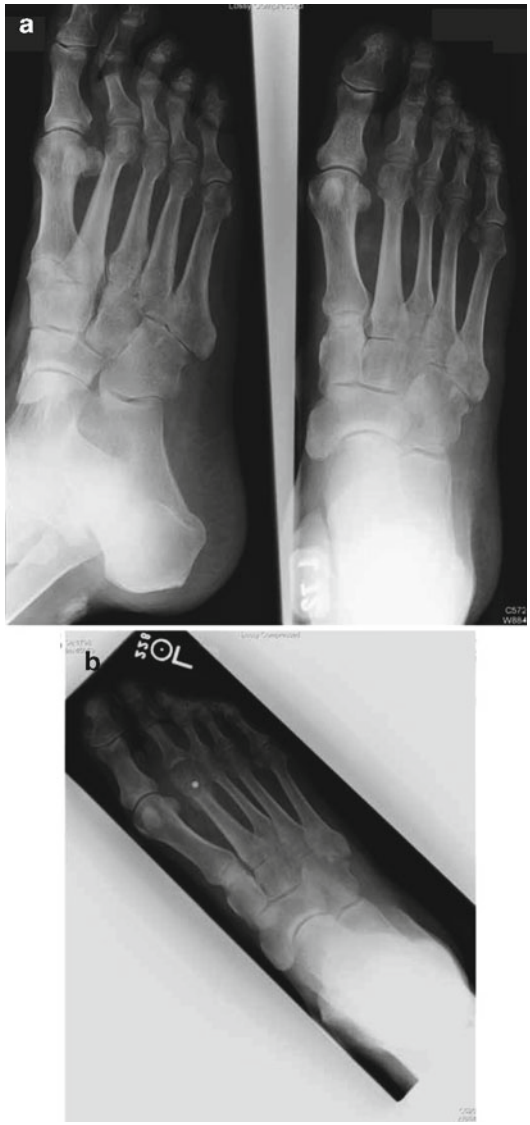

Fig. 17.8 An alternative osteotomy is the Weil where the bone cut is directed at a 45° angle from a dorsal distal to plantar proximal direction and is fixated with a single 2.0 cortical screw

allow for more even distribution of weight-bearing forces across all metatarsal heads. Shoe gear modification may also assist in this role.

Lesser Metatarsal Head Resection with Ulcer Excision

An alternative approach for relieving plantar pressure is to resect the offending metatarsal head entirely. While this will result in resolution of the ulceration, this carries a high incidence of transfer lesion or ulceration. For this reason, it is preferred to perform this procedure only when osteomyelitis of the metatarsal head is suspected and there is no alternative but to resect the offending metatarsal head.

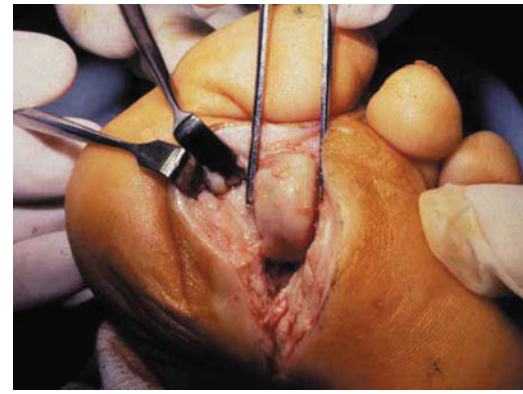

Fig. 17.9 An osteomyelitic lesser metatarsal head can be resected through a plantar elliptical incision excising the ulceration in toto

Resection of the metatarsal head can be approached through a dorsal linear incision centered directly over the metatarsal head. It should be remembered that the base of the corresponding proximal phalanx should also be resected as this structure is contiguous with the metatarsal head and is also involved. The ulcer is then allowed to heal by secondary intention.

An alternate approach is to resect the metatarsal head through a plantar approach while excising the ulceration. The advantage of this approach is that all necrotic and infected tissue can be excised and all tissue be directly inspected (Fig. 17.9). Following resection of the metatarsal head, the wound can be closed primarily as described for 1st MTPJ resection.

The postoperative care requires that sutures are left in place for a minimum of 3 weeks and the patient is kept totally non-weight bearing for 3–4 weeks. The patient is maintained on oral antibiotics until the sutures are removed. Long-term complications include possible transfer lesions or ulcerations and stress fractures due to the altered weight-bearing surface. It is therefore recommended that patients be fitted with an appropriate orthotic device to distribute pressures evenly.

Panmetatarsal Head Resection

Weight-bearing forces are designed to be evenly dispersed across all metatarsal heads. This weight-bearing interdependence between the metatarsal heads has been previously described first by Morton and later by Cavanagh [15, 16]. Disruption of this relationship will alter normal weight distribution. This can occur from trauma to the metatarsals resulting in dorsiflexed or shortened metatarsals as seen in stress fractures, the atrophic form of Charcot joint resulting in dissolution of metatarsal heads or prior surgical resection of metatarsal heads for osteomyelitis.

The recidivistic nature of diabetic foot disease makes multiple metatarsal procedures common in this patient population. Osteomyelitis of multiple metatarsal heads was previously treated by transmetatarsal amputation. This procedure was popularized by Dr. Leland McKittrick of the New England Deaconess Hospital and was responsible for saving thousands of limbs [30]. It is not without its complications however. Ulcerations at the distal stump and equinovarus contractures are common long-term complications (Fig. 17.10a, b). Patients have difficulty psychologically accepting this procedure because it will often require special shoe gear that draws attention to the fact they have had an amputation.

The panmetatarsal head resection and its variations were originally described for the treatment of painful lesions in patients with rheumatoid arthritis [31–34]. Jacobs first described the use of the panmetatarsal head resection for the successful treatment of chronic neuropathic ulcerations [35]. This report was subsequently followed by a report by Giurini et al. where a larger series of patients were studied and an alternate technique was described [34]. Similar success rates were cited. Over the years, the panmetatarsal head resection has replaced the TMA as the procedure of choice in patients with recurrent ulcerations following prior surgical resection of metatarsal heads [36, 37].

The primary indication for the panmetatarsal head resection is the presence of chronically recurrent neuropathic ulcerations on the plantar aspect of the foot following prior metatarsal head resections or ray amputations. It is our belief that

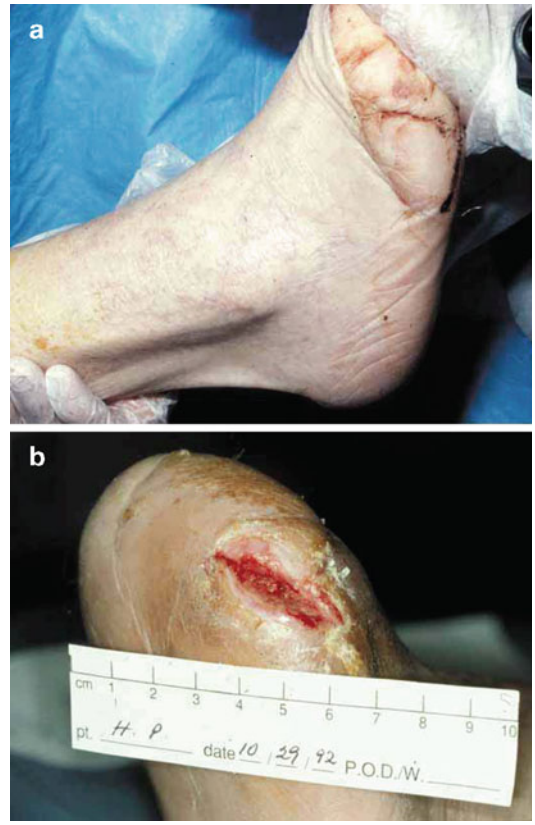

Fig. 17.10 (**a**) A common complication following transmetatarsal amputation is contracture of the Achilles tendon and subsequent equinus deformity. This can lead to characteristic lesions at the distal end of the TMA. (**b**) A distal lateral ulceration of a TMA with an underlying equinovarus deformity

if two or more metatarsals have already been resected or need to be resected to eliminate osteomyelitis, the patient would be best served by a panmetatarsal head resection (Fig. 17.11). At first, this may appear to be a drastic, aggressive approach. However, experience has shown that this approach may actually spare patients additional trips to the operating room for transfer ulcerations.

Various surgical approaches have been described for the panmetatarsal head resection. Dorsal approaches, plantar approaches or a combination of the two have been performed with equal success [38]. When possible the preferred approach is the four incision dorsal approach: one incision directly over the 1st metatarsal, one

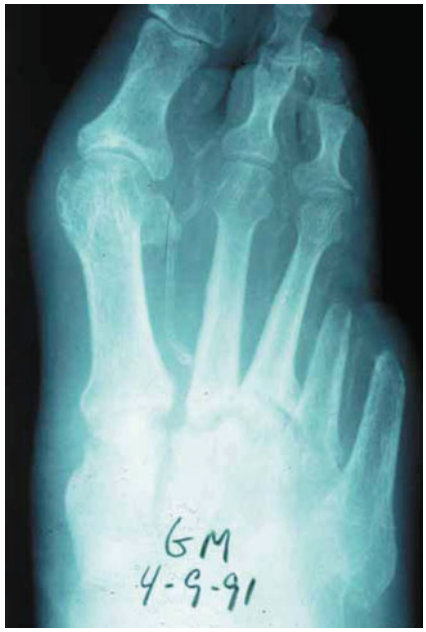

Fig. 17.11 Prior resection of two metatarsal heads and the presence of osteomyelitis of a remaining metatarsal head is indication for panmetatarsal head resection

between the 2nd and 3rd metatarsals, one directly over the 4th metatarsal, and one directly over the 5th metatarsal. This approach has the following advantages: allows adequate exposure of all metatarsal heads, decreases the potential for retraction injury on the skin edges, and maintains adequate skin islands so as not to affect vascular supply. Because the primary indication for this procedure is the presence of an open ulceration with osteomyelitis, the most common approach is to combine a dorsal incision with a plantar incision which excises the ulceration. The plantar wound and all necrotic tissue can then be excised, the involved metatarsal head(s) can be resected and the wound closed primarily as previously described.

The surgical technique for resection of the metatarsal heads has already been described. The most important technical point to remember in performing this procedure is to maintain the metatarsal parabola. This typically means that the 1st and 2nd metatarsals are left approximately the same length while the 3rd, 4th, and 5th metatarsals are each successfully shorter. Failure to maintain this relationship can lead to recurrent ulceration and additional surgery. If a prior metatarsal head resection or ray amputation has already been performed, then a perfect parabola may not be achievable. In that case, the metatarsal parabola should be recreated with the remaining metatarsals. Additionally, the extensor tendons are identified and are retracted. This will maintain the function of these tendons during the gait cycle affording this procedure the prime advantage over the TMA.

Midfoot Procedures

Surgery in the region of the midfoot is most commonly necessary following foot deformities resulting from neuroarthropathic (Charcot) joint disease. The most common location of Charcot joint involves the tarsometatarsal (Lisfranc's) joints but other joints in the midfoot may also be affected [39, 40]. Instability of Lisfranc's joint often results in a rocker-bottom deformity of the midfoot with plantarmedial ulceration. This is primarily due to subluxation of the 1st metatarsal and medial cuneiform creating a plantar prominence. Ulcerations on the plantar and lateral aspect of the foot are not uncommon. These result from plantar extrusion of the cuboid from a Charcot process at the calcaneocuboid joint [41]. These pose a significant management problem, as they are typically recalcitrant to conservative measures. There is no single surgical procedure that can be applied to all ulcers in this location. Therefore, a flexible approach to these lesions is required. Surgical approaches may involve simple ostectomy with or without fasciocutaneous flap or primary arthrodesis of unstable joints.

Ostectomy

This is the simplest approach to chronic plantar ulcerations of the midfoot. This is reserved for those deformities that have their apex directly plantar to the 1st metatarsal-medial cuneiform joint and where the midfoot is not hypermobile.

The depth of the ulceration will dictate the best surgical approach. A direct medial incision which is centered over the joint is preferred when the ulceration is superficial and not involving

bone. This will allow for excellent visualization of the joint and the prominent bone. The prominence can then be resected from medial to lateral either with an osteotome or with a saw. The goal should be to remove an adequate amount of bone to alleviate the plantar pressure and not create a new bony prominence which could create a new source of irritation and ulceration, thus negating the benefits of this procedure.

Ulcerations which communicate with bone and show signs of osteomyelitis clinically are best managed by excision of the ulceration with bone resection and primary closure of the ulceration. In addition to removing the infected bone, the ability to close the ulceration primarily without tension is an additional goal. This approach can be used when the ulcer is located either plantar central or plantar lateral in the midfoot. The most likely etiology for these ulcerations is plantar displacement of the cuboid. When the ulceration measures less than 2.5 cm, this surgical approach can be used. The use of closed suction irrigation is also recommended in order to prevent hematoma formation which can lead to wound dehiscence or infection.

One of the more difficult ulcerations to manage is an ulcer located centrally in the midfoot secondary to plantar subluxation of the cuboid bone. This is the type 5 of the Harris and Brand classification of Charcot joint disruption (pattern II in the Sanders classification) and has been described as being very resistant to conservative care [39, 40]. Resolution of these ulcerations often requires surgical intervention of some type.

Exostectomy with Fasciocutaneous Flap

When ulcerations of this type exceed 2.5 cm in diameter, primary excision with closure is often not possible and an alternate technique must be sought [41]. Ulcerations of this size are typically excised circumferentially to the level of the cuboid bone. This will allow removal of all necrotic, infected tissue as well as any hyperkeratotic margins bordering the ulcer. The joint capsule and periosteum of the cuboid are next encountered which are reflected off the underlying cuboid. This will expose the peroneal groove of the cuboid bone. The peroneus longus will often be found running in the groove. When possible this should be retracted so as to protect it from inadvertent injury. On rare occasions, however, it may be necessary to sacrifice the peroneus longus in order to gain adequate exposure of the bony prominence. The peroneal groove is next resected with the use of an osteotome and mallet. Once completed, the wound should be carefully inspected for any remaining bony prominence or bone spicules which can serve as a new point of pressure and possible ulceration.

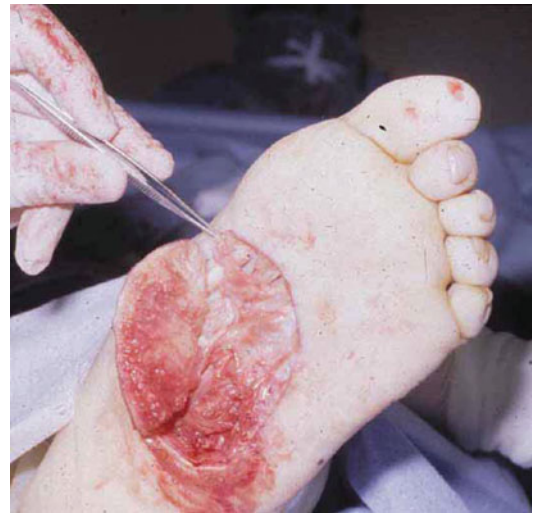

Fig. 17.12 The flexor digitorum brevis muscle is commonly used for closure in large plantar ulcerations following ulcer excision and exostectomy of the offending bone

This procedure will often leave a relatively large dead space which can serve for the collection of a hematoma. It is best to fill this dead space with a muscle flap which will serve two purposes: (1) it will decrease the dead space following the bony resection; (2) it will provide a layer of soft tissue between the underlying bone and the overlying skin (Fig. 17.12). The flexor digitorum brevis muscle is well suited for this purpose because of its anatomic location and ease of dissection. The muscle is rotated laterally to cover the cuboid. A full thickness fasciocutaneous flap which is based on the medial plantar artery is then rotated from medial to lateral to cover the actual ulcer site. A split thickness skin graft is then used to cover the donor site in the medial arch (Fig. 17.13).

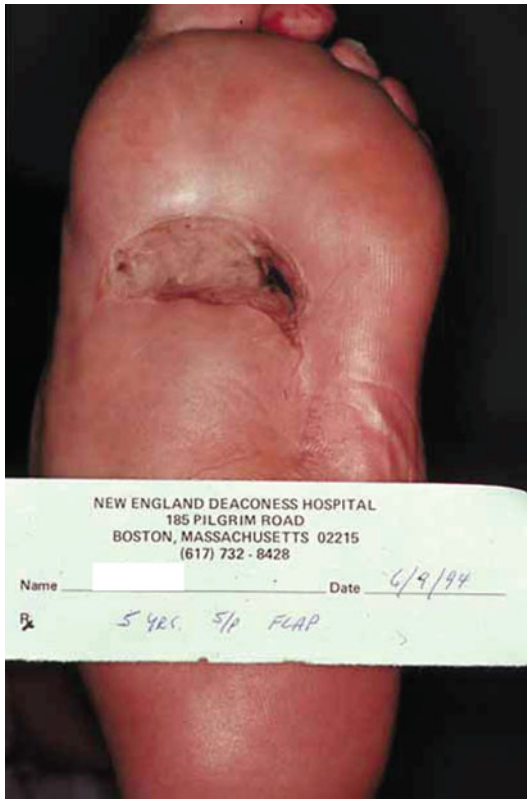

Fig. 17.13 A patient who is 5 years status post cuboid exostectomy with an interpositional muscle flap and a rotational fasciocutaneous flap

Six weeks of total non-weight bearing is required for adequate healing and incorporation of the flap. This is followed by an additional 2–4 weeks of protected weight bearing in a surgical shoe with a molded orthotic device. Long-term care will require the use of plastizote orthoses and modified shoe gear.

Advancement or rotational flaps of the foot have become relatively infrequent since the introduction of negative pressure wound therapy (NPWT), also referred to as vacuum assisted closure (VAC). Negative pressure wound therapy was first introduced in the United States in 1997 [42, 43]. Since its introduction, it has been extensively used in large circumference wounds with significant depth in order to promote granulation, decrease the number of dressing changes and avoid more extensive and morbid procedures. As a result, there has been a significant reduction in the number of rotational flaps or free tissue transfers needing to be performed. Newer designs of NPWT have concentrated on making the device smaller and more portable [44].

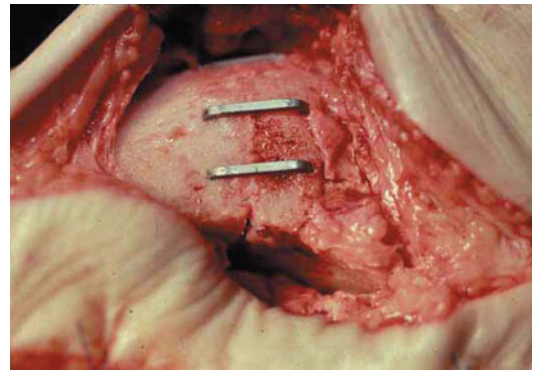

Fig. 17.14 Fusion of the 1st metatarsal-medial cuneiform joint for an unstable Charcot joint complicated by recurrent ulceration can be achieved by use of staples

Medial Column Fusion

When resolution of the Charcot joint process has resulted in significant bone loss such that there is significant instability at the 1st metatarsal-medial cuneiform joint, primary fusion of this joint should be considered. Simple exostectomy in the presence of instability will often fail due to continued collapse of this segment, resulting in a new bony prominence. Stabilization of this joint therefore is the better alternative.

The joint can be approached surgically through a direct medial incision. This will afford adequate exposure of the dorsum of the joint as well as the plantar surface. The articular cartilage on both sides of the joint is resected with a sagittal saw. It is recommended that the bone cut on the 1st metatarsal side be slightly angulated from dorsal-proximal to plantar-distal. This will plantarflex the 1st metatarsal slightly, restoring the weight-bearing function of the first ray. In addition, it is recommended that any plantar bony prominence also be resected from medial to lateral.

Fixation of the joint can be achieved in a variety of ways. While crossed .062 Kirschner wires and staples are acceptable means of fixation, the authors prefer either a medial plate with an interfragmentary screw or crossed screws to provide rigid internal fixation and compression (Figs. 17.14

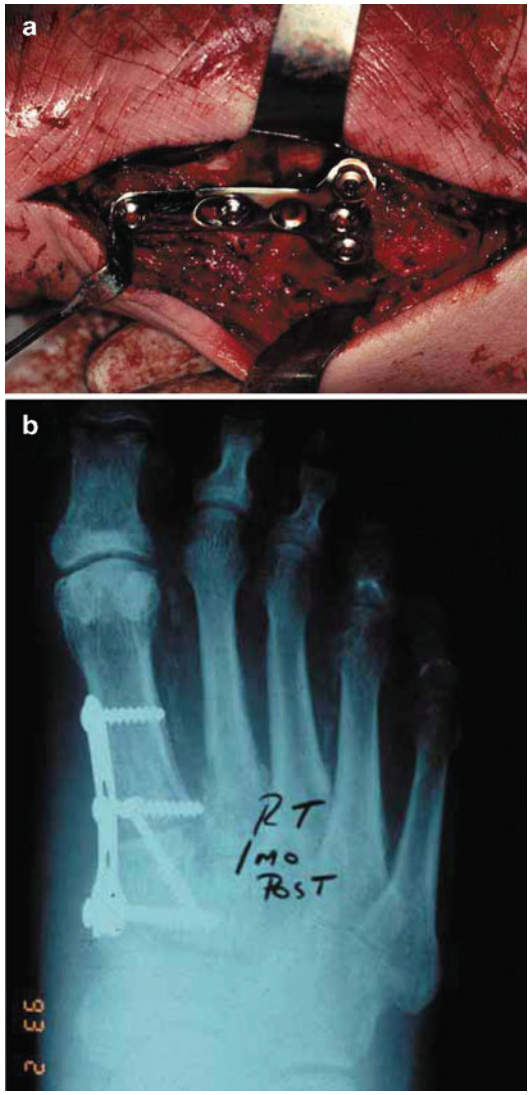

Fig. 17.15 (**a**) A T-plate with an interfragmentary screw is another acceptable form of fixation of the 1st metatarsal-medial cuneiform joint in the presence of unstable Charcot joint. (**b**) Radiograph of patient with T-plate and interfragmentary screw across the 1st metatarsal-medial cuneiform joint

and 17.15a, b). Recently we have been using an intramedullary rodding technique which will be described later in this chapter. It is advisable to insert a Jackson-Pratt drain to prevent the accumulation of an hematoma.

The postoperative course requires immobilization and non-weight bearing. While there is no standard length of immobilization and non-weight bearing, the patient can expect to be non-weight bearing on average 3 months. Partial weight bearing may begin when serial X-rays show early trabeculation across the 1st metatarsal-medial cuneiform joint. Continued resumption of weight bearing is allowed as long as both clinical and radiographic evaluations suggest continued healing of the fusion site.

Charcot joint disease can also affect the entire Lisfranc's joint complex, i.e., all five tarsometatarsal joints. This is commonly referred to as multiarticular involvement. In the case of severe midfoot instability stabilization of the entire midfoot may be necessary. These procedures will be covered below under hindfoot procedures.

Hindfoot Procedures

Surgical procedures of the hindfoot are most commonly performed for reconstruction of unstable Charcot joint disease and can be truly classified as limb salvage procedures. These include partial or subtotal calcanectomy, tendo-Achilles lengthening, triple arthrodesis, and pantalar arthrodesis. We will also include multisegmental midfoot arthrodeses.

Indications for these reconstructive procedures include chronic, nonhealing ulcerations with underlying hindfoot deformity or instability, severe instability of the hindfoot making ambulation difficult at best, or chronic heel ulcerations with underlying osteomyelitis. Because of the high-risk nature of these procedures, all conservative measures should be attempted prior to intervening surgically or when the only alternative is a major limb amputation.

Calcanectomy

Heel ulcerations a common event in patients with diabetes. Due to the comorbid conditions most diabetic patients display, periods of prolonged bedrest is not unusual. Without proper protection decubitus ulcerations can occur. However other causes for heel ulcers include blisters from shoe or cast irritation and heel fissures resulting from dry skin or puncture wounds. Regardless of the

precipitating cause, the end result is prolonged disability and morbidity. In cases of bone involvement (i.e., osteomyelitis), below knee amputation can be the final outcome. Attempts to save this extremity to provide a limb capable of functional ambulation can involve excision of the ulceration and the calcaneus, either partial or subtotal.

The goals of the calcanectomy should include excision of all necrotic and infected soft tissue, resection of any and all infected bone and primary closure of the wound whenever possible. Additional bone resection may be necessary in order to achieve primary closure. Hindrances to primary closure can include the lack of mobility of the surrounding soft tissue and severe tissue loss from infection. In these cases, a more creative approach may be necessary. This can include rotational skin flaps, free tissue transfers, or NPWT.

The majority of times this procedure is performed for osteomyelitis. It is therefore critical that adequate bone is removed to eliminate the infection. It is also important that no plantar prominence be left behind which could serve as an irritant to the soft tissue and result in ulceration. In resecting the calcaneus the Achilles tendon is often encountered. Depending on the extent of infection, it may need to be debrided or even released. While one may be tempted to reattach the tendon, it is rarely advisable to do so. Advancement of the Achilles tendon would require the introduction of foreign materials such as screws or anchors which could serve as a nidus of recurrent infection. In those cases where the Achilles tendon is detached, it will often fibrose to the surrounding tissues and provide some degree of plantarflexion (Fig. 17.16a, b).

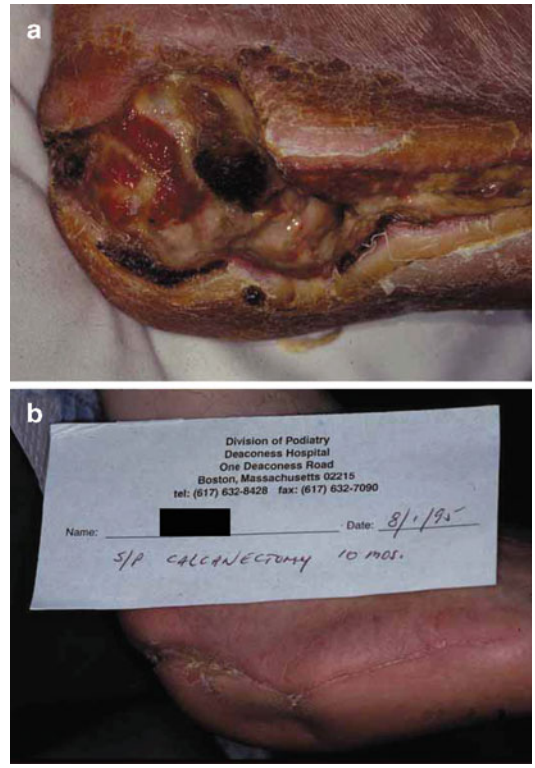

Fig. 17.16 (**a**) Osteomyelitis of the calcaneus with resultant soft tissue loss is a common cause of lower limb amputation. (**b**) Same patient following partial calcanectomy with excision and debridement of infected, necrotic tissue and primary closure. Successful eradication of infected bone resulted in limb salvage

Tendo-Achilles Lengthening

Over the past 5 years there has been increasing literature on the effect of a tight Achilles tendon on foot ulcerations and Charcot joint disease [45]. It has been well documented that patients with diabetes develop increased glycosylation of skin and soft tissue structures, including tendons [27]. This then leads to increased plantar foot pressures. A tight Achilles tendon from enzymatic glycosylation has been implicated as a contributing factor not only in forefoot ulcerations but in the development of Charcot joint disease. Whether the Achilles tendon becomes tight as a result of the Charcot joint disease or a tight Achilles tendon contributes to the development of Charcot joint disease remains a matter of great discussion. In the end, all authors agree that a tight Achilles tendon contributes to the recurrent nature of these problems and should be addressed via tendon lengthening [46–48].

There are several techniques to lengthen the Achilles tendon. These can be classified as either open or percutaneous [49]. The simplest and least morbid technique is the percutaneous approach. This technique uses three small stab incisions and minimal soft tissue dissection. However, this

requires an understanding of the anatomy of the Achilles tendon and the ability to convert to the open technique when necessary. The Achilles tendon is formed by the end fibers of the gastrocnemius and soleus muscles and insert into the dorsal posterior aspect of the calcaneus. By virtue of its insertion, the Achilles tendon functions as a strong plantarflexor at the ankle joint and invertor of the subtalar joint. Its plantarflexion motion is opposed by the extensor muscles crossing the anterior aspect of the ankle joint and its inversion motion is opposed by the peroneal muscles laterally. When the calcaneus everts and the axis of the subtalar joint changes as occurs in patients who excessively pronate, the axis of pull of the Achilles tendon also changes [18]. It now creates a strong pronatory force of the foot. This can lead to excessive medial transfer of weight and midfoot collapse as seen in Charcot joint disease. It is for this reason that the Achilles tendon must be evaluated in every case of Charcot joint disease and reconstructive surgery. Failure to recognize this fact can lead to recurrence of the ulceration and failure of the reconstruction.

The percutaneous technique is the simplest, least morbid procedure to lengthen the Achilles tendon. The procedure can be approached with the patient lying either supine or prone. Three small stab incisions are made centrally on the Achilles tendon (Fig. 17.17). The incisions will be spaced approximately 1.5–2.0 cm apart with the distal most incision being 1.5 cm from the insertion of the Achilles on the calcaneus. The most proximal and most distal incisions will incise the Achilles centrally and exit laterally while the middle incision will incise the Achilles centrally and exit medially. Once the three incisions are completed, a gentle dorsiflexion force is exerted on the foot until a gentle stretch can be felt on the Achilles. Care should be taken not to stretch the Achilles beyond 10° of dorsiflexion. The skin incisions are then closed with suture of the surgeon's choice.

While the percutaneous technique provides adequate correction and is the least morbid technique, there are situations where greater degrees of correction are needed. This is where the open technique may be needed. This is best performed

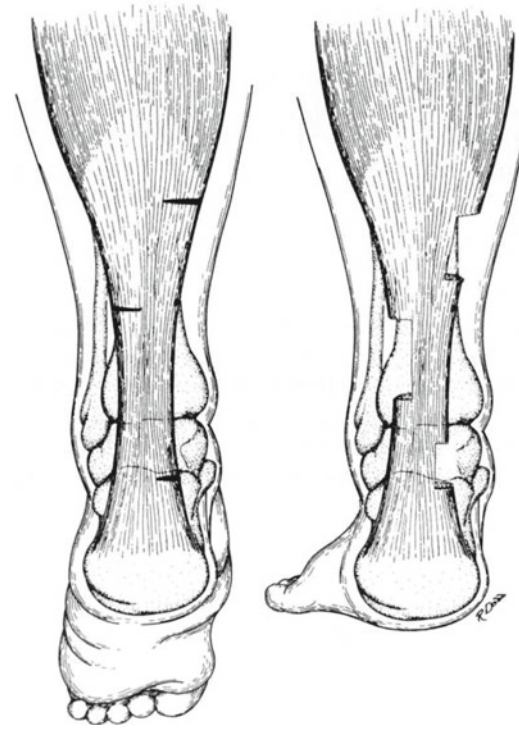

Fig. 17.17 The percutaneous technique uses two medial stab incisions and one lateral incision. The ankle is dorsiflexed to allow for lengthening of the Achilles tendon

with the patient prone. An approximately 8–10 cm incision is made along the central portion of the Achilles tendon. The incision is deepened until the peritenon is visualized. The peritenon is incised longitudinally along the line of the skin incision exposing the Achilles tendon. While there have been several ways described to lengthen the tendon, our preferred method is to make one incision approximately 1.0 cm proximal to the insertion. The blade is inserted into the midsubstance of the Achilles all the way across and the anterior fibers are transected. Attention is then directed approximately 2.5–3.0 cm proximally where the blade is once again inserted into the midsubstance of the Achilles tendon. The posterior fibers of the tendon are now transected. Once completed, the foot is once again gently dorsiflexed until the tendon can be seen to lengthen along the central intact fibers (Fig. 17.18). In this fashion, the surgeon can visualize the amount of lengthening achieved and

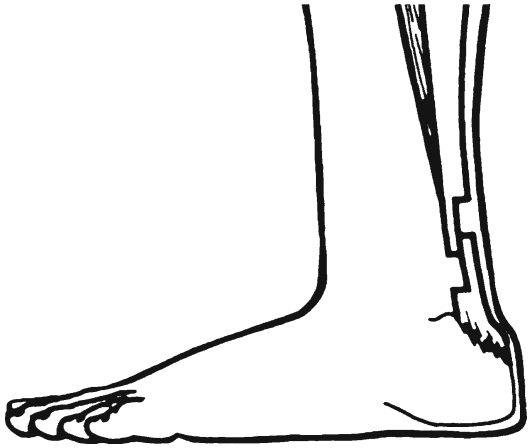

Fig. 17.18 The open Achilles tendon lengthening creates incisions proximally and distally. The tendon is then lengthened in the frontal plane

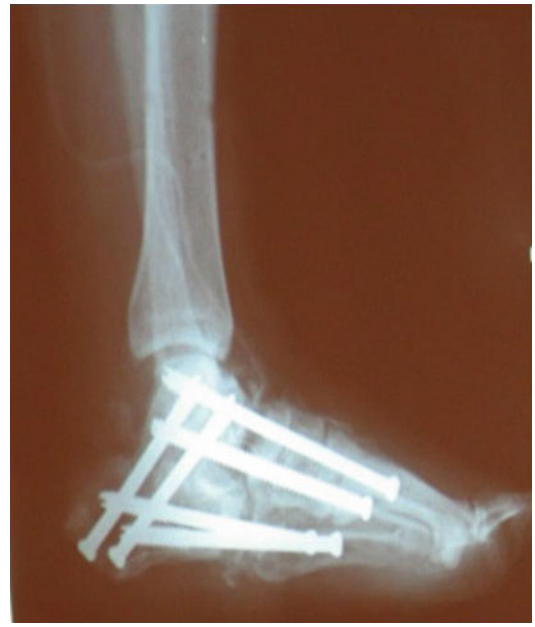

Fig. 17.19 The intramedullary rodding technique introduces large diameter screws through the metatarsals and across the hindfoot joints to achieve stability, primary fusion and deformity correction

"dial-in" more dorsiflexion if necessary and if feasible. Closure of the wound, including the peritenon, is performed in a layered fashion. The Achilles tendon lengthening is protected for approximately 6 weeks in a splint or brace that maintains the ankle joint at 90°.

Midfoot Arthrodesis

The most common location for Charcot joint disease is the tarsometatarsal joints, i.e., Lisfranc's joints. These are the joints formed by the metatarsal bases and the cuneiforms and cuboid bone. These joints are supported by several small ligaments that connect these bones to each other. While the inciting event for the development of Charcot joint disease remains unclear, in the majority of cases disruption of these ligaments with or without fractures is a common feature. Because of absence of pain, the patient continues to ambulate on this unstable foot resulting in further destruction, displacement and instability. The end result is a foot that is grossly misshapened, unstable to walk on, and at risk for ulceration, infection, and amputation. While initial treatment should consist of non-weight bearing, immobilization, and bracing, many feet are so unstable that bracing actually poses a risk to the patient. It is in these cases that surgical intervention should be contemplated.

Earlier in this chapter, we described one technique of surgical reconstruction consisting of medial column fusion, either with screws or plates. This works well when destruction is limited to the 1st metatarsal-medial cuneiform joint. However, when the entire midfoot is involved and there is dorsal displacement of the midfoot on to the hindfoot, a more aggressive approach relocating the entire midfoot is needed [50, 51]. Over the past 5 years we have employed a technique where the medial and lateral columns of the midfoot are rodded with large screws that are inserted through the intramedullary canals of the 1st metatarsal and the 4th metatarsal (Fig. 17.19). These screws cross the tarsometatarsal joints into the respective tarsal bones. In those cases where the talonavicular joint is also involved, a single long screw can be used to cross both the 1st metatarsal-medial cuneiform joint and the talonavicular joint as part of a triple arthrodesis. The screws are inserted following appropriate resection and realignment of the involved joints.

This intramedullary rodding technique has the advantage of providing adequate realignment and compression of the affected joints. This is a very stable construct. The other advantage is it avoids excessive dissection of the joints. With the introduction of cannulated screws and using intraoperative X-rays, these screws can be accurately placed through small stab incisions, avoiding large wounds and excessive stripping of the periosteum which can compromise healing of these fusion sites.

Triple Arthrodesis

The incidence of Charcot joint disease involving the tarsal joints—talonavicular, calcaneocuboid or subtalar—ranges from 1.8 to 37% depending on the reports [52–54]. Clinically, these feet may appear with a rocker-bottom deformity from plantar subluxation of the talonavicular joint or the calcaneocuboid joint. This can then lead to chronic ulceration. When faced with a significant degree of instability from this destructive process, the approach should include surgical stabilization of the involved joint or joints. This often requires fusion of the talonavicular joint, calcaneocuboid joint, and the subtalar joint, i.e., triple arthrodesis.

The goal of a triple arthrodesis is to stabilize the foot and to reduce the deformity, thereby reducing the risk of recurrent ulceration. The surgery should be delayed until the acute phase has resolved and the Charcot joint has entered the coalescent phase. If an open ulceration is present, surgery should be delayed until all signs of acute infection are resolved.

The triple arthrodesis is performed in a standard fashion [55]. The calcaneocuboid joint is approached through a lateral incision just inferior to the lateral malleolus and extending distally to the base of the 4th and 5th metatarsals. While it is possible to obtain adequate exposure of the talonavicular joint through this incision, one should not hesitate to make a separate incision medially if this affords better exposure.

The cartilage is resected off all joint surfaces until bleeding bone is exposed. The joints are then reapproximated. If significant deformity exists, wedge resections through the joints may be required to adequately reduce the deformity. Additionally, significant bone resorption may have occurred as a result of the destructive process. In these cases, bone graft may be necessary to fill the gaps between joint surfaces. This can be obtained from the iliac crest or from the bone bank.

The method of fixation is the surgeon's choice. Typically, the posterior subtalar joint is fixated with a 6.5-mm cancellous screw. This screw can be introduced from a dorsal approach through the talar neck or a small stab incision can be made on the plantar surface of the heel. The screw is then inserted from plantar to dorsal, across the subtalar joint into the body of the talus. This latter technique is preferred. While screws are preferred for the talonavicular and calcaneocuboid joints, staples can also be used. Recently, a small claw plate has been introduced to arthrodese the calcaneocuboid joint. Adequate apposition of joints and accurate placement of fixation devices is achieved by the use of intraoperative X-rays. The goal of surgery is correction of the deformity with good apposition of all joint surfaces. Minimal to no gapping should be present. This should always be confirmed with a final intraoperative X-ray to confirm the final position of all fixation devices, adequate joint apposition and appropriate foot position. The position of the calcaneus should be neutral to slight valgus.

Postoperatively, the patient is initially placed in a posterior splint to immobilize the fusion site. This is replaced with a below the knee fiberglass cast usually 4–5 days following surgery. Total non-weight bearing is maintained for a minimum of 3–4 months. Serial X-rays are obtained to evaluate bone healing and maintenance of postoperative correction and alignment. The patient is then advanced to gradual protected weight bearing when X-rays show signs of bone union. Case reports suggest that the likelihood and rate of fusion may be improved with the use of electrical bone stimulation, although prospective, randomized, double-blinded trials are needed to determine overall efficacy [56].

Pantalar Arthrodesis

The ankle joint that has undergone severe destruction from Charcot joint disease is

particularly problematic. This typically will result in an ankle joint so flail that it makes ambulation extremely difficult if not impossible. This deformity may result from total collapse of the talar body, fractures through the medial malleolus, lateral malleolus, or both. Patients with these types of fractures will often be found ambulating directly on either the medial or lateral malleolus. This inherent instability will result in the development of chronic ulcerations and are extremely difficult to control with conservative care alone. The prognosis for these deformities is poor. In order for limb salvage to be achieved, primary fusion of the ankle and subtalar joints is necessary.

The surgical approach depends on the level and degree of destruction. If the primary level of instability and destruction involves the tibiotalar joint, isolated fusion of this joint may be sufficient. However, if destruction of the other rearfoot joints is present, then fusion of the ankle, talonavicular, subtalar, and calcaneocuboid joints (i.e., pantalar fusion) should be performed. All surgical intervention should be delayed until all signs of acute Charcot joint disease have resolved. Attempted fusion during the active, hyperemic phase of this disorder not only will make fusion technically difficult but may also result in failure to fuse.

A lateral incision which begins approximately at the midfibula and extends to the tip of the lateral malleolus offers adequate exposure of the ankle joint. If a pantalar fusion is to be performed, this incision can be extended distally to the calcaneocuboid joint. The fibula is typically osteotomized just proximal to the ankle joint line. The anterior aspect of the fibula is dissected free and reflected posteriorly. This preserves the vascular supply to the fibula. This will allow the fibula to be used as a vascularized strut graft on the lateral side of the ankle joint. The ankle joint is now well visualized.

The articular cartilage is resected down to bleeding cancellous bone from the inferior surface of the tibia and the dome of the talus. The ankle joint is repeatedly manipulated so as to assess alignment of the foot. The joint surfaces are continually remodeled until optimal bone apposition and foot alignment is achieved. In cases where the talar body is deemed nonsalvageable, a femoral head allograft has been used to fill in any defect or accommodate for significant bone loss. If a pantalar fusion is being performed, the remaining hindfoot joints can be addressed at this time in the same manner as in a triple arthrodesis.

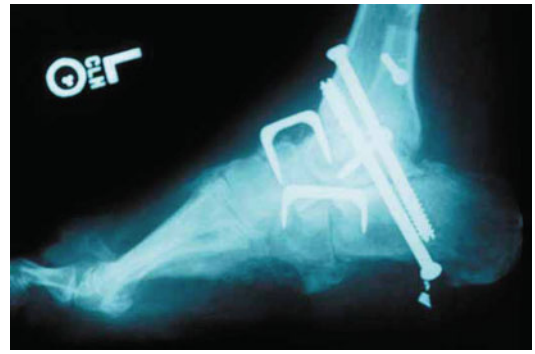

Fig. 17.20 Severe instability of the rearfoot due to Charcot joint often requires major reconstructive surgery of the hindfoot and ankle. A pantalar fusion was performed in this patient for severe cavoadductovarus deformity and chronic ulceration resulting from Charcot joint. Two 7.0 mm cannulated screws were used to fuse the subtalar and ankle joints

After all articular surfaces have been resected, the foot should be positioned so that all bone surfaces are in good apposition with minimal to no gapping. Care should also be taken to avoid any interposition of soft tissue. If the foot cannot be aligned properly or bone surfaces do not appose adequately, further remodeling of the bone should be performed. Once optimal alignment has been achieved, the ankle joint is ready for fixation. Internal fixation of the ankle joint can take one of two forms. This can be performed with the introduction of two 7.0 mm cannulated screws. These are typically inserted from a plantar to dorsal direction through the body of the calcaneus and across the resected ankle joint. This will also fixate the posterior subtalar joint (Fig. 17.20). Ideally, the tips of the screw should purchase the cortex of the tibia. An alternate technique is the use of a retrograde intramedullary nail which is also introduced across the ankle and subtalar joints from a plantar approach

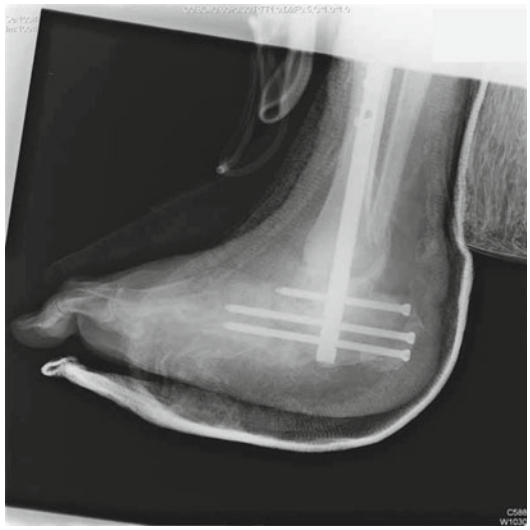

Fig. 17.21 X-ray showing Charcot ankle reconstruction using an intramedullary nail and femoral head allograft

(Fig. 17.21). When bone quality precludes the use of internal fixation, external devices for fixation are appropriate alternatives. The use of intraoperative imaging is critical in the placement of guide wires and for final fixation. It is critical that the calcaneus be positioned either in neutral or in slight valgus position. Any degree of varus should be avoided. After fixation of the ankle joint, the remaining rearfoot joints can be fixated as previously described.

As with triple arthrodesis, the postoperative care is critical to successful limb salvage. Wound infection, dehiscence, and nonunion are the major complications seen with this procedure. Immobilization of the extremity immediately postoperatively can decrease the risks of these complications. Total non-weight bearing in a fiberglass below the knee cast is required for a minimum of 4–6 months. The fusion site must be protected with cast immobilization and casts must be changed frequently to prevent abrasions or cast irritations. Once it is felt fusion is sufficient to support weight bearing, this should be instituted in a gradual protected manner. A return to protected weight bearing will be dictated by serial X-rays. The use of adjunctive modalities to promote fusion, such as electrical bone stimulation, should be considered in this patient population as these patients and procedures are considered at high risk for nonunion.

Arthrodesis with External Fixation

The complex nature of these deformities has recently required utilization of recent advances in external fixation [57–60]. As previously stated, the degree of bone loss in these hindfoot deformities will often not allow for dependable use of internal fixation devices. In addition, the presence of an open ulceration and osteomyelitis makes the use of internal fixation contraindicated. It has therefore become necessary to use various external fixation constructs to achieve stabilization of these deformities without the inherent risks of internal fixation [61]. The most common construct utilizes a combination of multiplane fine wire ring fixators, half pins, and foot plate attached to the leg and foot at different levels [62]. If possible, this can be used in conjunction with internal fixation (Fig. 17.21).

Resection of joints and devitalized bone is performed as previously described. The resected joints can be wedged to allow for as near anatomic alignment as possible. The use of bone graft is often necessary for proper alignment and to make up for large defects. Once the foot is reduced into an anatomic alignment, a series of thin wires are placed proximal and distal to the osteotomy. The proximal wires are generally inserted through the calcaneus and the talus, while the distal wires are generally passed through the metatarsal shafts. These wires will then be connected to the foot plate and tensioned. This will provide compression across the osteotomy site, whether it is in the midfoot or hindfoot. Additional wires and ring fixators are inserted through the distal tibia. The rings are then connected to each other by a series of bolts. This configuration will then provide increased stability and rigidity of the lower extremity. There are times when the external fixator is used in combination with an intramedullary rodding technique. While this provides a very stable construct, the insertion of the skinny wires is more challenging and critical.

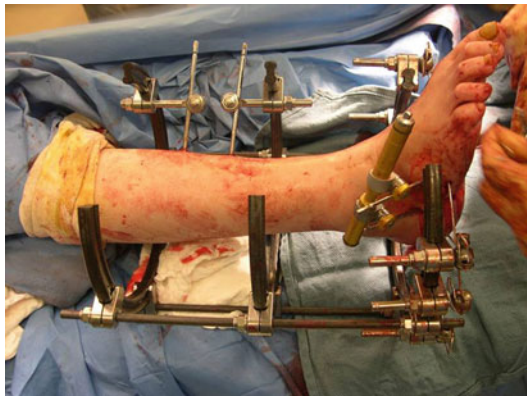

Fig. 17.22 Severe Charcot deformity with an open ulceration and osteomyelitis will require the use of external fixation to correct the deformity and to avoid the use of internal fixation at the site of ulceration and osteomyelitis

The advantage of this technique is that it allows the reconstruction of severe deformities where there have been large degrees of bone loss and large degrees of instability. The thin wires are used to bridge these defects and insert the fixation into better quality bone. This technique can also be used in the face of open ulcerations or where osteomyelitis had been present since the external wires can be inserted at sites remote from the site of ulceration and infection (Fig. 17.22).

The major disadvantages of this technique are the bulkiness of the device itself, the risk of pin tract infections and the inability to apply a compression dressing leading to significant edema. The external fixator is usually in place for approximately 3 months. During this time, the patient finds it difficult to be mobile. It can also interfere with sleep and irritate the contralateral extremity. Showering is also a problem. The exposed wires are also vulnerable to bending and irritation of the surrounding skin, making pin tract infections possible. It is therefore important that meticulous pin care is performed (Fig. 17.23a, b).

In spite of these disadvantages, many patients will choose to undergo this extensive procedure, as the only other option is a major limb amputation.

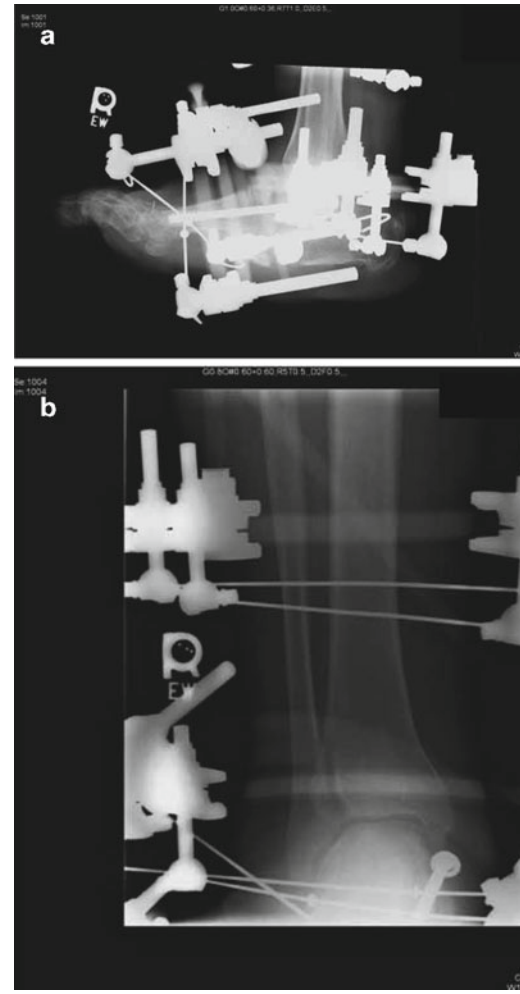

Fig. 17.23 (**a**) Charcot reconstruction demonstrating correction with combination of internal and external fixation to address midfoot and hindfoot deformities (*lateral view*). (**b**) External ring fixator using thin wire technique (*AP view*)

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Microbiology and Treatment of Diabetic Foot Infections

18

Adolf W. Karchmer

Abstract

Foot infections in diabetic patients are a major source of morbidity and an important proximate cause of amputations. These infections can be categorized clinically as limb threatening or non-limb threatening. The former are often caused by *Staphylococcus aureus* (often methicillin-resistant) and group B streptococci while the latter by these organisms and gram-negative bacilli and anaerobes. Multidrug-resistant pathogens are found in chronic infections, especially after exposure to health care and antibiotics. Effective treatment combines appropriate antimicrobial therapy with wound management and, if needed, surgical debridement. Osteomyelitis is common, often requiring surgical debridement for effective therapy. Although aspects of care could be refined by additional study, current evidence is sufficient to prevent or effectively treat most of these infections.

Keywords

Foot infection • Osteomyelitis • *Staphylococcus aureus* • Methicillin-resistant *S. aureus* • Multidrug-resistant bacteria • Infected ulcers • Amputations

The foot of patients with diabetes mellitus is affected by several processes which not only contribute to the development and progression of infection but on occasion alter the appearance of the foot in ways that may obscure the clinical features of local infection. Neuropathy involving the motor fibers supplying muscles of the foot causes asymmetric muscle strength, which in turn results in foot deformities and maldistribution of weight (or pressure) on the foot surface. Dysfunction of the sensory fibers supplying the skin and deeper structural elements of the foot allows minor and major injury to these tissues to proceed without appreciation by the patient. As a result of neuropathy, the foot may be dramatically deformed, ulcerate in areas of unperceived trauma (mal perforans), and on occasion be warm and hyperemic in response to deep structural injury (acute Charcot's disease). This warmth and hyperemia

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may be misinterpreted as cellulitis and an ulceration, while a major portal of entry for infection may be uninfected. In the patient with diabetes, peripheral neuropathy may develop in isolation or commonly in parallel with atherosclerotic peripheral vascular disease. The latter involves major in-flow vessels to the lower extremity but commonly is associated with occlusive lesions of the tibial and peroneal arteries between the knee and ankle. The resulting arterial insufficiency can alter the appearance of the foot and obscure infection. Rubor may reflect vascular insufficiency rather than inflammation and conversely pallor may mute the erythema of acute infection. Gangrene and necrosis may be primarily ischemic or may reflect accelerated ischemia in the setting of infection. In sum, the diagnosis of infection involving the foot in patients with diabetes requires a careful detailed examination of the lower extremity and its blood supply.

The Diagnosis of Foot Infections

The initial step in the diagnosis of a foot infection in a patient with diabetes is to recognize those patients at greatest risk and to suspect infection. Clinical factors that have been significantly associated with foot infection include peripheral vascular disease with absent arterial pulses or an ankle brachial index of <0.9, loss of protective sensation, a history of recurrent foot ulcers or prior amputation, foot ulcers of >30 days duration, a wound that extends to bone, i.e., a positive probe to bone test (see Sect. "Osteomyelitis"), and a traumatic wound [1, 2]. Thereafter, infection is diagnosed clinically and to varying degrees supported by test results. Finding purulent drainage (pus) or two or more signs or symptoms of inflammation (erythema, induration, swelling, pain, tenderness, or warmth) is indicative of infection. Clinical signs on occasion belie the significance and severity of infection. A minimally inflamed but deep ulceration may be associated with underlying osteomyelitis [3]. Serious limb-threatening infection may not result in systemic toxicity. For example, among patients hospitalized for limb-threatening infection only 12–35% have significant fever [4–6]. In fact, fever in excess of 102°F suggests infection involving deeper spaces in the foot with tissue necrosis and undrained pus, extensive cellulitis, or bacteremia with the potential for hematogenous seeding of remote sites. Laboratory studies may be supportive of the diagnosis of these infections but must be interpreted in the context of clinical findings. Thus, the erythrocyte sedimentation rate and C-reactive protein concentration may be normal in infected patients and in up to 50% of patients with deep foot infection the white blood cell count may be normal [7]. Elevated concentration of C-reactive protein and procalcitonin can help distinguish mild or moderately infected ulcers from those that are uninfected [8]. Open skin wounds and ulcerations are often contaminated or colonized by commensal organisms that on occasion become pathogens. As a consequence, cultures while essential in the assessment of the microbiology of foot infections, do not in isolation establish the presence of infection. Unless the cultured material is obtained from deep tissue planes by percutaneous aspiration, the results of cultures must be interpreted in the clinical context.

The Severity of Foot Infections

Multiple classification schema have been designed to define the severity of foot wounds with or without infection in patients with diabetes. Some such as the widely used Wagner system include infection only in one grade [9]. Others, focused on subtle grading of features of infection, require a scoring sheet and are thus too complex for routine clinical use. The Infectious Diseases Society of America (IDSA) classification utilizes depth of a wound, presence of ischemia, presence and extent of infection, and systemic toxicity to designate the severity of foot infection. This schema classifies wounds from having no infection to being severely infected (Table 18.1) [10]. Increased severity in the IDSA classification schema, e.g., moderate and severe infection, correlates with the need for hospitalization and amputation [11].

Table 18.1 Classification of severity of diabetic foot infection

Clinical manifestation of infection	Infection severity[a]
Wound lacking purulence of any manifestations of inflammation	Uninfected
Presence of ≥2 manifestations of inflammation (purulence, or erythema, pain, tenderness, warmth, or induration), but any cellulitis/erythema extends ≤ 2 cm around the ulcer, and infection is limited to the skin or superficial subcutaneous tissues; no other local complications or systemic illness	Mild
Infection (as above) in a patient who is systemically well and metabolically stable but which has ≥ 1 of the following characteristics: cellulitis extending > 2 cm, lymphangitic streaking, spread beneath the superficial fascia, deep-tissue abscess, gangrene, and involvement of muscle, tendon, joint or bone	Moderate
Infection (moderate) in a patient with systemic toxicity or metabolic instability (e.g., fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia, or azotemia)	Severe

Adapted from ref. [10] with permission
[a] In the setting of severe ischemia, all infections are considered severe

A simple practical classification of foot infection into limb-threatening or non-limb threatening has also been described [12]. In this schema, infection is categorized primarily based on depth of the tissues involved, this being largely function of depth of a predisposing ulceration, and the presence or absence of significant ischemia. Patients with non-limb-threatening infection have superficial infection involving the skin, lack major systemic toxicity, and do not have significant ischemia. What might have been a non-limb-threatening infection becomes limb threatening in the face of severe ischemia. In a non-limb-threatening infection, an ulceration does not penetrate fully through skin. Limb threatening infection, when not categorized as such based on severe ischemia, involves deeper tissue planes with the portal of entry being an ulcer which has penetrated at least into subcutaneous tissue or potentially deeper to tendon, joint, or bone. Although limb threatening infections may be dramatic with extensive tissue necrosis, purulent drainage, edema, and erythema, they may be cryptic as well. Thus, an infected deep ulcer with a rim of cellulitis that is ≥2 cm in width is considered limb-threatening. Of note, hyperglycemia occurs almost universally in patients with non-limb-threatening and limb-threatening infection. In contrast, significant fever occurs in only 12–35% of patients with limb-threatening infection [4–6]. Fever is found primarily in these patients with extensive cellulitis and lymphangitis, infection (abscesses) loculated in the deep spaces of the foot, bacteremia, or hematogenously seeded remote sites of infection.

Mild or less extensive moderate infection by the IDSA guidelines would be considered non-limb-threatening infection in this simplified schema. Infection categorized by the IDSA schema as more extensive moderate or severe would be judged limb-threatening infection in this simplified schema. The simple classification, when adjusted for prior medical therapy and antibiotic exposure which is likely to result in infection by resistant organisms, allows one to anticipate the organisms causing wound infections and thus is an excellent point of departure from which to plan empiric antimicrobial therapy.

Microbiology

Cultures of open foot ulcers cannot be used to establish the presence of infection. Foot ulcers whether infected or not will contain multiple commensal or colonizing bacteria, some of which have the potential to become invasive pathogens. As a foot ulcer transitions from uninfected to infected, organisms isolated from the ulcer cavity include both colonizing flora and invasive pathogens. Assigning specific significance to organisms isolated from ulcers may be difficult. Sapico and colleagues demonstrated that the organism cultured from specimens obtained by aspiration or by curettage of the base of a cleansed ulcer were most concordant with those isolated from necrotic infected tissue excised from adjacent to the ulcer

base [13]. Of note, cultures of aspirated material failed to yield pathogens recovered from curettage or excised tissue in 20% of patients. Although not endorsed strongly by the IDSA guidelines or other experts, culture of material obtained on swabs of the deep ulcer base may provide useful information. Slater, et al., found that in wounds that did not extend to bone essentially the same organisms were recovered from cultures of swab specimens and deep tissue specimens. When wounds extended to bone, swab cultures recovered only 65% of organisms cultured from deep tissues [14]. Pellizzer et al. also found that on initial wound cultures swab specimens taken from deep in the ulcer yielded the same bacterial species as did cultures of deep tissue biopsies, with the exception that *Corynebacterium* species, likely colonizers or contaminants, were isolated from swab cultures [15].

Although the microbiology from clinical reports, wherein most specimens are obtained through the ulceration, requires interpretation to adjust for the inclusion of organisms of known low invasive potential and likely to be commensals or colonizers, it is possible to sense the major pathogens causing non-limb-threatening and limb-threatening foot infections. When surgical or aspiration specimens are not readily available for culture, antibiotic therapy can be designed with reasonable confidence based upon the culture results from specimens obtained by curettage of the ulcer base. Accordingly, culture of material obtained from an ulcer base by curettage, after the ulcer has been cleansed and debrided is recommended. Culture of material swabbed from an ulcer base is a less desirable alternative. The exception to the utility of cultures obtained from ulcers is in the design of antimicrobial therapy for osteomyelitis when the infected bone is to be debrided piecemeal, as opposed to resected en bloc. In this situation, more precise biopsy based culture information is highly desirable [10, 16].

In non-limb-threatening infections, particularly those occurring in patients who have not previously received antimicrobial therapy, *Staphylococcus aureus* and streptococci, particularly group B streptococci, are the predominant pathogens [10, 16–20]. *S. aureus* has been isolated from more than 50% of these patients and in more than 30% *S. aureus* is the only bacterium isolated [17]. Recently, as in other skin and soft tissue infections, *S. aureus* causing infections in the feet of diabetics are increasingly methicillin-resistant (MRSA), the prevalence increasing from 11.6 to 21.9% from 2003 to 2007 in one study [21]. Other studies have also noted an increase in the percent of *S. aureus* that are methicillin-resistant [22–24].

Limb-threatening foot infections, which often involve deeper tissues and are typically chronic as well as previously treated, are generally polymicrobial. Cultures from these infections yield on average 2.3–5.8 bacterial species per culture. Both gram-positive cocci and gram-negative rods are commonly isolated from a single lesion and in 40% of infections both aerobic and anaerobic organisms are recovered [4, 10, 13, 16, 18, 20, 25–27] (Table 18.2). Individual cultures have yielded on average 2.9–3.5 aerobes and 1.2–2.6 anaerobes [28]. *S. aureus* (including methicillin-sensitive and methicillin-resistant isolates), streptococci (particularly group B streptococci), and facultative gram-negative bacilli (*Proteus* species, *Enterobacter* species, *Escherichia coli*, *Klebsiella* species) and *Pseudomonas aeruginosa* are the predominant pathogens in these infections. Among the anaerobes, *Peptostreptococcus* species, *Prevotella* species, and *Bacteroides* species, including those of the *B. fragilis* group, are recovered frequently [28, 29]. Of note, *Clostridium* species are recovered infrequently. Although anaerobes are recovered from 41 to 53% of limb-threatening infections in clinical trials, with optimal methods these organisms can be recovered from 74 to 95% of these infections [28]. The frequency of isolating anaerobic bacteria is greatest in those patients with the most severe infections, particularly those where infection involves necrotic gangrenous tissue and amputation is often required. Nevertheless, the clinical features of foot infections, beyond those which allow categorization as non-limb threatening or limb threatening, are not sufficiently sensitive clues to allow defining the specific microbiology of these infections. Fetid infections suggest infection

Table 18.2 Microbiology of limb-threatening infections in patients with diabetes[a]

Organisms	Percent of patients (number patients)						
	Gibbons et al. (42)	Hughes et al. (50)	Bamberger et al. (51)	Scher et al. (65)	Grayson et al. (96)	Citron et al. (427)	Gadepalli et al. (80)
Aerobic							
S. aureus	22	25	22	23	54	15	14
S. epidermidis	12	14	19	18	12	11	8
Enterococcus spp.	16	17			28	12	11
Streptococcus spp.	13	20	41	54	55	10	
Corynebacterium spp.	7		8			7	
E. coli	7	3	1	19	6	1	12
Klebsiella spp.	4	7	4	10	5	2	7
Proteus mirabilis	11	11	5	36	9	2	13
Enterobacter spp.	3	7	7		9	2	1
Other							
Enterobacteriaceae	2	5	7	50	17	2	10
P. aeruginosa	3	0	5	15	8	2	9
Acinetobacter spp.	1	0	0		7	1	
Anaerobic							
Gram-positive cocci	21	40	14	52	12	13	7
Bacteroides fragilis		5	4			3	7
Bacteroides melaninogenicus		11				4	
Other							
Bacteroides spp.	6	2	5	55	30	3	
Clostridium spp.	2	1	3	23		1	1
Other anaerobes		13	2	20	14	6	3
Number isolates/infection	2.76	3.62	2.88	5.76	2.77	3.8	2.3

Data from refs. [4, 25–27, 51, 63, 72]

[a] Specimens obtained by various routes, including deep ulcer swabs, curettage of the ulcer base, aspiration, or tissue biopsy

with anaerobes; however, anaerobes including *B. fragilis* may be recovered from infections that are not particularly foul smelling. Hence, clinical clues beyond the major categorization of infections are not sufficient to predict the microbiology of foot infections.

The spectrum of bacterial species recovered from foot infections, especially those that are limb threatening, can be dramatically altered by prior failed antimicrobial therapy or contact with the health care system. While *P. aeruginosa*, *Acinetobacter* species, *Enterobacter* species, and other antibiotic-resistant facultative gram-negative bacilli (some of which are resistant by virtue of extended-spectrum beta-lactamase production) are uncommon in previously untreated infections, these organisms are not infrequent isolates from infected chronic ulcers [4, 27, 30]. Similarly, MRSA may be encountered commonly in patients with chronically infected foot ulcers that have persisted in spite of multiple prior courses of antimicrobial therapy or in patients with extensive health care requirements, e.g., chronic dialysis, hospitalization for comorbid conditions, residence in skilled nursing facilities or particularly those with a prior history of infection with this organism [31]. These resistant bacteria are probably acquired nosocomially or alternatively emerge from endogenous flora during hospitalization or repetitive antibiotic treatment of patients with nonhealing foot ulcers. Accordingly, when selecting an antimicrobial regimen to treat a foot infection in a patient who has had contact with the health care system or prior courses of antibiotics, physicians should anticipate the presence of antibiotic-resistant pathogens.

The role of relatively avirulent bacteria, many of which are part of skin flora that are often isolated from cultures of specimens obtained through

an ulcer, is uncertain. *Staphylococcus epidermidis* and other coagulase-negative staphylococci have been recovered, usually in conjunction with other bacteria, from 15 to 35% of these infections and may reflect ulcer colonization. On the other hand, *S. epidermidis* has been isolated on occasion from deep tissue as the only organism suggesting these organisms may be pathogens in some patients. Enterococci, viridans streptococci, and *Corynebacterium* species, organisms that are often considered contaminants and not pathogens when isolated from skin and soft tissue infections, are among the isolates recovered frequently from polymicrobial limb-threatening foot infections. When recovered from specimens in conjunction with typical pathogens, these organisms are often disregarded as contaminants [10, 16]. Often, foot infections respond to therapy with antimicrobials which are active in vitro against the pathogens but not against these presumed contaminants [28, 32]. These observations support the designation of these organisms as contaminants; alternatively, they could indicate that with the eradication of major pathogens, host defenses and surgical debridement can control these less virulent organisms. On occasion enterococci, viridans streptococci, or *Corynebacterium* species are isolated from uncontaminated specimens and may even be the sole bacterial isolate from an infection [18]. Thus, these organisms too should not be routinely disregarded but rather interpreted in the clinical context.

Microbiologic Assessment

Clinically uninfected ulcers should not be cultured. When infection is present, a microbiologic diagnosis will usually facilitate subsequent therapy, particularly in the setting of limb-threatening infection or that occurring after failure of prior antimicrobial therapy [5, 12, 19]. While cultures of tissue obtained aseptically at surgery or purulent specimens aspirated percutaneously are more likely to contain only true pathogens, obtaining these specimens before initiating therapy is often either impractical or not feasible (no abscess present). Accordingly, before beginning antibiotic therapy the skin should be cleansed and any overlying eschar debrided. Then specimens for culture should be obtained by curettage of the necrotic base of the ulcer. Specimens should be handled and processed as both routine wound cultures and primary anaerobic cultures. As noted, specimens obtained by swabbing deep in the ulcer or from curretted tissue in the base of the ulcer may provide a reasonable assessment of infecting organisms [14, 15, 33]. If patients have been febrile recently, blood cultures should also be obtained before initiating antimicrobial therapy. With subsequent debridement during early days of therapy, specimens from necrotic purulent tissue or exposed bone should be recultured. Concurrent antimicrobial therapy may preclude isolation of susceptible organisms during effective therapy; however, resistant organisms missed on the initial cultures can be recovered from these later debridement specimens [15]. Treatment of osteomyelitis involving bones in the forefoot that will be totally resected does not require specific bone cultures, that is antibiotic therapy can be designed using the results of appropriate wound cultures. If en bloc resection of the involved bone, i.e., foot sparing amputation, is not performed, more precise microbiologic data from bone biopsy would be desirable to allow selection of optimal antibiotic for therapy [10, 16, 34]. Biopsy of abnormal bone underlying infected ulcers is generally safe and in severely neuropathic patients may not require anesthesia. Infected bone in the midfoot or posterior foot that can be probed or that lies beneath an ulcer and appears infected on imaging studies should be biopsied for culture and histopathology, ideally either surgically or using fluoroscopic guidance through a route other than the ulcer [10, 16, 34]. Here, where debridement is likely to be piecemeal, rather than en bloc resection of all involved bone, precise microbiologic data from bone is required so that optimal antimicrobial therapy can be selected. Alternatively, bone that remains unexposed after debridement and wherein osteomyelitis is not strongly suspected based on radiologic findings may not be biopsied, but rather the infection is treated as if it is limited to soft tissue. Careful clinical and radiologic follow-up of this

bone in 2–4 weeks will often resolve the question of osteomyelitis without the potential hazards of an invasive procedure.

Treatment

Debridement and Surgery

With the exception of cellulitis or lymphangitis arising from an unrecognized (or microscopic) portal of entry, infected foot lesions generally require debridement. Debridement should be done surgically rather than by chemical or enzymatic agents [35]. Urgent surgical intervention is required when patients present with foot infection complicated extensive necrosis or gangrene, crepitus or gas in tissues on imaging, necrotizing fasciitis (or pain out of proportion to findings thus suspected necrotizing fasciitis), critical ischemia, or life-threatening sepsis. For apparent non-limb-threatening infections, debridement may be limited but nevertheless allows full evaluation of the portal of entry and prepares the site for culture. Occasionally, what appeared to be a non-limb-threatening infection is discovered on debridement to actually be limb-threatening with extension of infection to deep tissue planes. Limb-threatening infection by virtue of extension to deep tissue planes requires surgical debridement [5, 12]. Early surgical intervention can reduce the duration of hospitalization and the need for major amputations [36]. Failure to decompress involved compartments and debride necrotic tissue and drain purulent collections increases the risk of amputation [5, 12, 36, 37]. Percutaneously placed drains or aspiration drainage is inadequate; rather, devitalized tissue must be resected and purulent collections drained by incision. Uncertainty about the patient's arterial circulation status should not delay initial debridement but should prompt an evaluation of arterial supply and a vascular surgery consultation. Effective debridement may require multiple procedures as the extent of tissue destruction becomes progressively more apparent. Optimal surgical treatment, that which minimizes tissue loss and results in a suitable weight-bearing foot, requires a thorough understanding of resulting foot function, avoidance of subsequent deformities that will predispose to recurrent ulceration, and recognition of the potential need for revascularization to insure healing [37]. The experience of the surgeon in this area and the availability of vascular surgery support are important in achieving optimal results [37]. If the infection has destroyed the function of the foot or if it threatens the patient's life, a guillotine amputation to allow prompt control of the infection with a subsequent definitive closure is advised [38].

Antibiotic Therapy

Antimicrobial treatment of foot infections in patients with diabetes is begun empirically and thereafter revised based upon the results of cultures, which were obtained prior to therapy and on occasion during therapy, plus the clinical response of the infection. Knowledge of the spectrum of bacteria which cause non-limb-threatening infection and limb-threatening infection, as well as the changes in these organisms that might have been induced by selected circumstances, e.g., prior antimicrobial treatment, serves as the basis for selecting effective empiric therapy. The potential toxicity of various antibiotics for individual patients and the unique vulnerability of patients with diabetes as a group must be considered. Thus, for this population with an increased frequency of renal disease, the availability of nonnephrotoxic antimicrobials with potent activity against gram-negative bacilli renders the aminoglycosides relatively undesirable and usually unnecessary. Antibiotic therapy is administered intravenously when patients are systemically ill, have severe local infection, are unable to tolerate oral therapy, or are infected by bacteria that are not susceptible to available oral antimicrobials. Some antimicrobials are fully bioavailable after oral administration, e.g., selected fluoroquinolones, clindamycin, and metronidazole, trimethoprim/sulfamethoxazole, and linezolid. When appropriate microbiologically and clinically, these could often be used in lieu of parenteral therapy initially. After control of infection,

continued therapy commonly can be effected with oral agents contingent upon the susceptibility of the implicated bacteria. For patients who require prolonged courses of parenteral therapy, e.g., for osteomyelitis, generally treatment can be provided in an outpatient setting [39].

Topical antimicrobials, including silver sulfadiazine, polymixin, gentamicin, and mupirocin, have been used to treat selected soft tissue infections; however, this approach has not been studied in foot infections. A cationic peptide antimicrobial, pexiganin acetate, used as a 1% cream applied topically was nearly as effective as oral ofloxacin in treating mildly infected foot ulcers [40]. Although antimicrobials have been applied topically to foot infections, it seems unlikely that the topical route would result in effective tissue concentrations of the antimicrobial. Accordingly, topical therapy should only be used to supplement effective systemic therapy and then with the realization that its efficacy is not established.

The potential therapeutic or prophylactic benefits of systemic antibiotic therapy in patients with uninfected neuropathic ulcers are a subject of debate. One controlled trial showed no benefit from antibiotic therapy [41]. In view of the potential adverse consequences, including colonization with resistant bacteria, antibiotic therapy is not recommended for clinically uninfected neuropathic ulcers [10, 35]. Similarly, continuation of antibiotics beyond a limited course that was sufficient to eradicate infection has not been required to accomplish the healing of ulcers that remain open [10, 17, 42].

Empiric therapy for patients with non-limb-threatening infection, many of whom can be treated as outpatients, is directed primarily at staphylococci and streptococci (Table 18.3) [10, 16, 20, 35]. Lipsky et al. demonstrated that oral therapy with clindamycin or cephalexin for 2 weeks in patients with previously untreated non-limb-threatening foot infection resulted in satisfactory clinical outcome in 96 and 86%, respectively [17]. Caputo et al. in a retrospective study reported that 54 of 55 patients with non-limb-threatening infections were improved or cured with oral therapy, primarily first-generation cephalosporins or dicloxacillin, directed at staphylococci and streptococci [19]. If patients with superficial ulcers present with more extensive cellulitis, that warrants hospitalization and parenteral antimicrobial treatment, cefazolin should be effective. However, if prior microbiologic data including known prior MRSA infection or colonization, exposure to the health care system, or other risk factors for infection caused by MRSA are present, infection caused by MRSA should be assumed and therapy should be initiated with vancomycin or another antimicrobial active against this organism. Linezolid, which is fully bioavailable when administered by mouth and thus can be given orally or intravenously, is generally active against MRSA and thus could be used for non-limb-threatening or limb-threatening foot infections [43]. Other antimicrobials active against MRSA available for intravenous administration in the setting of more extensive cellulitis include vancomycin, daptomycin, telavancin, and ceftaroline (a cephalosporin with activity against MRSA that has recently been approved by the FDA for treatment of complicated skin/soft tissue infection) [43–49]. The duration of treatment, which in the final analysis is determined by the time course of the clinical response, is usually 1–2 weeks.

Table 18.3 Selected antibiotic regimens for initial empiric therapy of non-limb-threatening foot infections in patients with diabetes mellitus

Antimicrobial regimen[a]
Cephalexin 500 mg p.o. q 6 h
Clindamycin 300 mg p.o. q 8 h
Amoxicillin-clavulanate (875/125 mg) one q 12 h
Dicloxacillin 500 mg p.o. q 6 h
Levofloxacin 500–750 mg p.o. q d
Moxifloxacin 400 mg p.o. q d
Trimethoprim/sulfamethoxazole DS, one or two tablets p.o. bid[b]
Linezolid 600 mg p.o. bid[b]

[a] Doses for patients with normal renal function

[b] Use if clinical information suggests possible methicillin-resistant *S. aureus* infection (MRSA). Trimethoprim/sulfamethoxazole may be less effective against streptococcal infection and require addition of second antimicrobial. Clindamycin is active against some MRSA

Multiple antibiotics have been demonstrated to be effective therapy in prospective treatment trials of complicated skin and soft tissue infections, many of which were foot infections. Additionally, some of these antimicrobials have been proven effective in prospective studies of foot infections, many of which have been limb threatening: amoxicillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam, ticarcillin-clavulanate, cefoxitin, ceftizoxime, ciprofloxacin, ofloxacin, moxifloxacin, imipenem/cilastatin, ertapenem, linezolid, daptomycin, telavancin, and ceftaroline [4, 32, 43, 46, 50–55]. In comparative prospective (sometimes blinded) trials of treatment for limb threatening foot infections, the clinical and microbiologic response rates for the studied agents have been similar and no single agent has been proven superior to all others [10, 16, 20]. A recent review examining patients across controlled trials suggested that carbapenem therapy was associated with fewer failures compared with multiple other antimicrobials but also noted the association of MRSA infection with failed therapy [56].

In selecting empiric therapy for limb threatening foot infections, reasonable principles emerge from clinical trials and other published studies [5, 10, 12, 16, 20, 35]. The choice of agents used empirically should be based upon the known polymicrobial nature of these infections with modification, where appropriate, to address anticipated highly resistant pathogens that might have been selected in the process of prior hospitalizations and treatment (Table 18.4) [57]. Given the high prevalence of MRSA, either acquired nosocomially or the so-called community acquired variant which has become commonplace, empiric therapy for limb threatening infection should include an agent effective against MRSA. These agents will also provide therapy for infections caused by streptococci, including Group B organisms. Additionally, empiric therapy should be effective against an array of Enterobacteriaceae including potentially multidrug resistant organisms when infection occurs in a chronic ulcer which has failed to heal despite treatment with multiple antibiotics. Anaerobes, including *B. fragilis*, should be treated empirically in the more severe infection where there is tissue necrosis and gangrene. Drug selection should attempt to minimize toxicity and be cost-effective. In limb-threatening infection (but not in life-threatening infection) initial empiric therapy does not have to be effective in vitro for all potential pathogens. Broad-spectrum therapy which is active against many, but not necessarily all, gram-negative bacilli, as well as against anaerobes, *S. aureus* and streptococci when combined with appropriate debridement and good wound care may be as effective as even broader spectrum antimicrobial therapy. Adequate debridement not only shortens required duration of therapy but is also required for effective therapy.

Empiric antimicrobial treatment should be reassessed between day 3 and 5 of treatment in the light of culture results and clinical response. When patients have responded clinically and therapy is unnecessarily broad spectrum (effective therapy for the bacteria isolated could be achieved by less broad-spectrum antimicrobials with possible cost savings, avoidance of toxicity, or a reduction in selective pressure for emergence of antimicrobial resistance), treatment regimens should be simplified based on culture data [10, 16]. If a bacterium resistant to the current therapy has been recovered and yet the clinical response is satisfactory, the treatment need not be expanded. This is true particularly for less virulent organisms and gram-negative bacteria; however, it seems imprudent to ignore MRSA. Alternatively, if in the face of an isolate resistant to treatment the response to therapy is unsatisfactory, the wound should be examined for undrained deep space abscess or necrotic tissue that has not been debrided, the adequacy of arterial circulation must be assessed, and because the resistant organism might be a pathogen (rather than colonizing flora), antimicrobial therapy should be expanded to treat this isolate.

A number of regimens have been recommended as reasonable initial empiric therapy of limb-threatening infections [10, 12, 16, 20]. Because of the potentially complex microbiology of limb-threatening infection and the emergence of a multiple drug resistant phenotype among these organisms, it is difficult to recommend a single or several regimens. Some antimicrobials that have been used to treat these infections in the past are,

Table 18.4 Antibiotics for empiric therapy of limb-threatening foot infection[a]

Antibiotic agent	Comments
Vancomycin	Active against streptococci, staphylococci including MRSA
Daptomycin	Active against streptococci, staphylococci including MRSA
Linezolid	Active against streptococci, staphylococci including MRSA
Telavancin	Active against streptococci, staphylococci including MRSA
Ceftaroline	Active against streptococci, staphylococci including MRSA and many Enterobacteriaceae (not ESBL producers, *P. aeruginosa)*
Levofloxacin	Active against streptococci and staphylococci (not MRSA) and many gram-negative bacilli
Moxifloxacin	Active against streptococci and staphylococci (not MRSA) and many gram-negative bacilli
Amoxicillin-clavulanate	Active against streptococci and staphylococci (not MRSA) and many gram-negative bacilli (not *P. aeruginosa*), also active against anaerobes
Piperacillin-tazobactam	Active against streptococci and staphylococci (not MRSA) and many gram-negative bacilli including *P. aeruginosa*, also active against anaerobes
Imipenem-cilastatin	Active against streptococci and staphylococci (not MRSA) and many gram-negative bacilli including *P. aeruginosa*, also active against anaerobes. Use when considering ESBL producing organisms
Ertapenem	Active against streptococci, staphylococci (not MRSA), many gram-negative bacilli including ESBL producers (not *P. aeruginosa*), active against anaerobes. Use when considering ESBL producing organisms
Ceftriaxone	Active against streptococci, staphylococci (not MRSA), and many gram-negative bacilli (not ESBL producers, *P. aeruginosa*, or anaerobes)
Cefepime/ceftazidime	Active against many gram-negative bacilli and *P. aeruginosa* (not against ESBL producers)
Metronidazole	Only active against anaerobes

ESBL extended spectrum beta-lactamase (use imipenem-cilastatin or ertapenem). Use doses suggested for complicated skin-soft tissue infection unless concomitant infection requires higher dose. Not all agents are approved by US Food and Drug Administration (FDA) for treatment of diabetic foot infections

[a]Often may need combined therapy, especially when considering MRSA and gram-negative bacillus polymicrobial infection

because of gaps in their spectrum of activity versus the typically anticipated pathogens, are no longer considered ideal when used alone: cefuroxime, cefamandole, cefoxitin, cefotetan, ceftazidime, ciprofloxacin. In patients with limb-threatening infections arising from chronic ulcers, particularly those who have had extensive prior antimicrobial therapy or medical care, highly antibiotic resistant pathogens should be anticipated. In general, empiric regimens should combine multiple antimicrobials proven effective in the treatment of complicated skin and soft tissue infection such that coverage includes relatively resistant gram-negative bacteria and MRSA and, in selected settings, anaerobes as well (Table 18.4).

Patients with life-threatening infections, e.g., those with hypotension or severe ketoacidosis, should be treated with maximal broad-spectrum regimens. These might include a carbapenem and an agent directed against MRSA plus, if highly resistant gram-negative bacilli are anticipated, gentamicin or another aminoglycoside can be added. Emergent debridement is essential for satisfactory outcome.

The duration of antimicrobial therapy for severe soft tissue foot infection is based upon the temporal response to wound care and antimicrobial therapy. Two weeks of therapy is often effective; however, some recalcitrant infections will require longer courses of treatment [4, 5, 10, 57]. After acute infection has been controlled, antimicrobial therapy that was begun parenterally should be changed to oral therapy with comparable orally bioavailable antibiotics. Even if the ulcer has not fully healed, antibiotics can in general be discontinued when evidence of infection has resolved [10, 16]. Persistent ulcers must be managed with wound care and avoidance

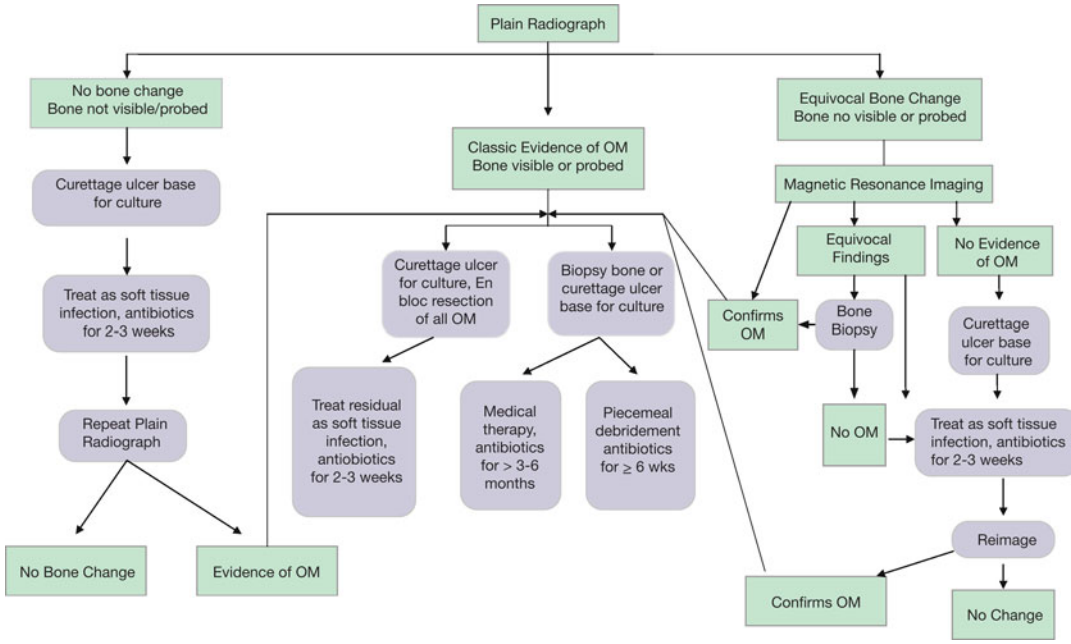

Fig. 18.1 An approach to the diabetic patient with suspected foot osteomyelitis (OM)

of weight bearing so that healing can be achieved and the ulcer eliminated as a portal for later infection. The occurrence of bacteremia, especially if remote sites are seeded, may require extended therapy. Of note, *S. aureus* bacteremia entails a distinct risk for secondary endocarditis as well as for seeding other sites such as bones, joints and the epidural space [58].

Osteomyelitis

The diagnosis of osteomyelitis is often difficult because of confounding Charcot neuroosteoarthropathy and adjacent soft tissue infection. In the diabetic foot osteomyelitis almost always results from direct extension through an overlying chronic infected ulcer. The diagnosis is reasonably certain if bone tissue (biopsy) is positive on culture and histopathology, there is purulence in bone at surgery, bone fragments are extruded, or a medullary abscess is noted on magnetic resonance imaging (MRI). Osteomyelitis is highly likely if there is visible or probe detected bone (probe to bone test) in a chronically infected ulcer, if MRI shows signs osteomyelitis, if bone tissue (biopsy) is positive by either culture or histology, but not both [6, 59]. MRI is the optimal imaging strategy for the diagnosis and determination of extent of osteomyelitis [6, 60–62]. However, the reported high sensitivity and specificity of this technique are derived from studies where the pretest probability of disease is very high and thus may be overstated if the technique is used more widely [62]. MRI imaging may be most useful in selected patients where suspicion of osteomyelitis is high but diagnostic uncertainty persists and bone biopsy is unattractive. Still the images must be interpreted with care by a knowledgeable radiologist. Nuclear isotope imaging is burdened by nonspecificity and anatomic imprecision and is not recommended [6, 61, 62]. Plain radiographs while useful as an initial step in evaluation of an infected foot, lack sensitivity and specificity. Serial radiographs over 2–4 weeks may provide evidence of osteomyelitis when in bone adjacent to an infected ulcer classic changes of infection develop in previously normal bone [6, 61, 62]. An approach to the diagnosis and treatment of the diabetic patient with suspected osteomyelitis is depicted in Fig. 18.1.

The therapy of osteomyelitis, which is one of the most debated and controversial areas in the treatment of foot infection, should coordinate antibiotic treatment with considerations of the surgical debridement of involved bone. Some reports have suggested that osteomyelitis of bones in the foot can be cured or at least arrested for extended periods with minimal debridement plus prolonged courses of antimicrobial therapy [6, 10, 16, 34, 52, 63–66]. Others have suggested that cure rates for osteomyelitis (particularly where bone destruction is evident or bone is visible or detectable by probing in an infected ulcer) will be enhanced by aggressive debridement, and even excision of all infected bone when feasible in the fore foot [5, 12, 36, 67].

A careful review of the literature on the treatment of osteomyelitis in the feet of diabetic patients concluded that no particular management strategy could be shown superior. This conclusion emerges because of heterogeneity in treated infections, diversity in the surgical approaches, biases in the selection of treatment modality, variability in antibiotic treatments and different definitions of outcome [59]. Decisions on when to use primarily medical versus aggressive debridement/resection surgical therapy in treating osteomyelitis is divided and is commonly based on physician experience. Nonsurgical management might be preferred when aggressive resection would lead to unacceptable foot dysfunction, limb ischemia precludes surgery, surgery carries excessive risk or is rejected by the patient, and osteomyelitis is limited to the fore foot (phalanges) with minimal soft tissue infection. If medical therapy fails, surgery may be required. More aggressive surgery is required if infection is life threatening or may be preferred if there is extensive bone necrosis, foot remodeling is required to correct bony prominences and improve function, the patient wishes to avoid very prolonged antibiotic therapy, or the potential toxicity of required antibiotic therapy can be minimized by aggressive surgery.

Selection of antibiotic therapy is ideally based on the precise microbiology of bone infection. Cultures from curettage of soft tissue deep in the infected ulcer overlying bone may suffice to design therapy when surgical resection of all infected bone is planned, i.e., therapy will be directed at residual soft tissue infection. However, when bone debridement will not be done or is limited, as in midfoot or calcaneous osteomyelitis, bone culture to define the microbiology is of paramount importance. Culture of soft tissue adjacent to bone does not adequately define bone microbiology [68]. Additionally, favorable outcome of therapy is more likely using antibiotics based on bone culture [65]. Adequate antibiotic therapy can be achieved by intravenous administration or the use of highly bioavailable oral agents. Specific antibiotic choices are contingent on pathogen susceptibility. Often sequential intravenous to oral therapy is used. The role of local therapy using antibiotic impregnated materials is not established [69].

Table 18.5 Duration of antibiotic therapy for osteomyelitis of pedal bone

Site/setting	Duration
Amputation with no residual infection	2–5 days after surgery
En bloc resection all infected bone with residual soft tissue infection	2–3 weeks
Residual infected bone (piecemeal debridement)	≥6 weeks after debridement
Medical therapy or after surgery with residual devitalized bone	3–6 months

[a]Adapted from ref. [10]

The duration of antibiotic treatment for osteomyelitis is based upon the amount of residual necrotic or infected bone and soft tissue (Table 18.5). If all infected bone is resected en bloc, e.g., amputation of a phalanges or phalanges and the related distal metatarsals, the residual infection has in essence been converted to a soft tissue process and can be treated accordingly, i.e., for 2–3 weeks [4, 5, 10, 12, 70]. In contrast, if osteomyelitis involves bones that cannot be resected en bloc without disruption of the functional integrity of the foot, debridement, if done at all, must be done in a piecemeal fashion. As a result, the adequacy of the debridement cannot be assured and the management strategy must be altered. In this situation pathogen-specific antimicrobial therapy should be administered for a prolonged period (at least 6 weeks) and adequate blood supply to infected tissues must be assured

[5, 10, 16, 34, 70]. Very prolonged antibiotic therapy has been used when medical cure is attempted in the setting of residual necrotic bone. The therapy has been given for 3–6 months and occasionally for a year [34, 59, 65, 66]. In every setting, the choice of a specific antimicrobial regimen and duration of therapy must be individualized and reflect not only local foot findings but also possible concomitant metastatic infection and potential adverse events.

When in spite of apparently appropriate treatment infection fails to respond and ulcers to heal, the foot should be reassessed for adequacy of arterial supply, persistence of necrotic soft tissue or bone requiring debridement, presence of a unresponsive or antibiotic resistant pathogen, or ineffective antibiotic delivery. Patient noncompliance with treatment or non-weight bearing must be considered as well. Therapy should be redesigned addressing defects found in the prior regimen.

Adjunctive Therapy

The effective treatment of foot infection is far more than the administration of antibiotics that are active in vitro against the implicated pathogens. Optimal therapy involves the integration of appropriate dressings and wound care, control of glucose metabolism, effective debridement and possibly reconstructive foot surgery. Non-weight bearing (off-loading) of neuropathic ulcers whether infected or noninfected is essential for healing. When ischemia is a limiting factor, vascular reconstruction may result in healing and foot salvage [35]. Many possible elements of adjunctive therapy are insufficiently evaluated to warrant inclusion in standard therapy. Hyperbaric oxygen therapy may facilitate healing but does not impact infection. The role of platelet-derived growth factor and bioengineered skin equivalent in healing has not been fully established. Treatment with granulocyte colony stimulating factor raises the peripheral white cell count and may accelerate slightly the control of a wound infection but has not become a standard component of care. Negative pressure dressings (vacuum-assisted closure or VAC dressings) in controlled trials have been shown to be safe and, in treating surgical wounds, to accelerate granulation tissue formation, reduce the time to wound closure, and yield a higher overall rate of wound healing [71]. Although widely used, they have not been generally recommended and their role in infected diabetic foot wounds is unclear. Topical antibiotics and antiseptics have not been demonstrated more effective than standard wound care and may cause local adverse reactions or promote emergence of resistance in bacteria. Accordingly, these have not been recommended.

Outcome

The knowledge and skills to achieve an optimal outcome in the treatment of diabetic foot infections often require the collaboration of multiple care providers, including diabetologists, infectious disease specialists, podiatrists, and vascular surgeons. With appropriate care a satisfactory clinical response can be anticipated in 90% of patients with non-limb-threatening infection and at least 60–80% of those with limb-threatening infection. Limb threatening infections may require foot-sparing amputations but salvage of a weight bearing foot is usually achievable. Vascular reconstruction, especially bypass grafts to pedal arteries which restore pulsable flow to the foot, decrease major amputations, and enable foot-sparing/foot-salvage surgery. Although the clinical science of treating diabetic foot infections has advanced significantly, challenges remain in defining optimal care. Still many foot infections could be prevented, effective therapy provided, and extremities salvaged if current knowledge was more widely applied.

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Lower Extremity Arterial Reconstruction in Patients with Diabetes Mellitus: Principles of Treatment

19

Bernadette Aulivola and Frank B. Pomposelli Jr.

Abstract

Lower extremity arterial occlusive disease is one of the most significant factors contributing to nonhealing ulceration, tissue loss, and the need for extremity amputation in the diabetic population. The most important principle in treating foot ischemia in these patients is recognizing that the cause is macrovascular disease of lower extremity arteries due to atherosclerosis. Knowledge of the appropriate evaluation and management of limb ischemia is of paramount importance in efforts toward limb salvage. Noninvasive testing and diagnostic arteriography play an important role in patient evaluation. Options for revascularization include endovascular techniques and surgical bypass. Revascularization planning is highly individualized and takes into consideration patient comorbidities and characteristics of the occlusive lesions.

Keywords

Arterial insufficiency • Revascularization • Arterial bypass • Angioplasty • Vascular disease

Introduction

Foot problems remain one of the most common reasons for hospitalization for patients with diabetes mellitus and account for a significant health care cost burden [1, 2]. According to the National Diabetes Fact Sheet, published in 2007 by the Centers for Disease Control, over 17 million people in the USA have been diagnosed with diabetes and an estimated 5.7 million more are yet undiagnosed [3]. Approximately 20% of diabetic patients can expect to be hospitalized for the treatment of foot complications at least once during their lifetime, accounting for an annual

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health care cost in excess of 36 billion dollars [1]. The primary pathologic mechanisms of peripheral neuropathy and ischemia set the stage for pressure necrosis, ulceration, and polymicrobial infection of the foot. If improperly treated, this process can ultimately lead to nonhealing ulceration, osteomyelitis, gangrene, and the need for amputation [4]. More than 60% of all nontraumatic lower extremity amputations are performed in diabetic patients. In 2004, approximately 71,000 lower extremity amputations were performed in diabetic patients in the USA [3]. Understanding the complex interplay of peripheral neuropathy, ischemia, and infection in the diabetic patient with a foot complication and providing proper treatment is essential to foot salvage. While this chapter focuses on the surgical treatment of ischemia due to arterial insufficiency, it is important to recognize that ischemia is accompanied by infection in approximately 50% of patients [5] and that most, if not all patients have a component of peripheral neuropathy as well. While focusing on the correction of ischemia using endovascular intervention or surgical bypass, the vascular surgeon must also address the complex pathobiology of the diabetic foot to ultimately be successful in limb salvage.

Vascular Disease in Diabetics

A detailed discussion of vascular disease in the diabetic patient can be found elsewhere in this book. Lower extremity peripheral arterial disease is one of the most significant factors contributing to the need for extremity amputation in this population. The incidence of arterial occlusive disease in the diabetic patient population is fourfold higher than in nondiabetics. The most important principle in treating foot ischemia in patients with diabetes is recognizing that the cause is macrovascular occlusion or stenosis of lower extremity arteries due to atherosclerosis. Historically, many clinicians incorrectly assumed that gangrene, nonhealing ulcers, and incomplete healing of minor amputations or other foot procedures, were the result of microvascular occlusion of the arterioles—the so-called small vessel disease [6]. This concept is erroneous and has been refuted in multiple studies [7–11]; however, it unfortunately persists to this day in some arenas. In the minds of many clinicians and their patients, this concept has resulted in a pessimistic attitude toward the treatment of ischemia that all too often lead to unnecessary major limb amputation without an appropriate attempt at arterial reconstruction. This attitude and approach is antiquated, inappropriate, and must be discouraged in the strongest of terms. In the authors' opinion, rejection of the small vessel theory alone could probably decrease the 40-fold increased the risk of limb amputation that diabetic patients face during their lifetime compared to their nondiabetic counterparts.

Atherosclerosis in Diabetes

Although histologically similar to disease in nondiabetics, atherosclerosis in the patient with diabetes has certain clinically relevant differences. Multiple previous studies have demonstrated that diabetes mellitus is a strong independent risk factor for atherosclerotic coronary [12, 13], cerebrovascular and peripheral arterial disease [14]. Patients with diabetes face a higher likelihood of cardiovascular mortality overall and possibly during the perioperative period after elective major vascular surgery [15]. In addition, generalized atherosclerosis is more prevalent, more severe and progresses more rapidly in diabetic patients [16]. Diabetics tend to present up to a decade earlier than nondiabetics with manifestations of their atherosclerotic disease. In those presenting with ischemic symptoms of the lower extremity, gangrene and tissue loss are more likely to be present in diabetics compared to nondiabetics. Also, diabetic patients with coronary atherosclerosis are more likely to have the so-called silent ischemia—absence of typical anginal symptoms or pain with myocardial infarction, particularly in those patients with significant polyneuropathy [17].

These findings suggest that arterial reconstruction in diabetic patients may carry a higher risk of adverse outcomes, particularly myocardial infarction and/or death. In fact, both Lee [18] and Eagle [19] have included diabetes mellitus as an independent risk factor for adverse cardiac

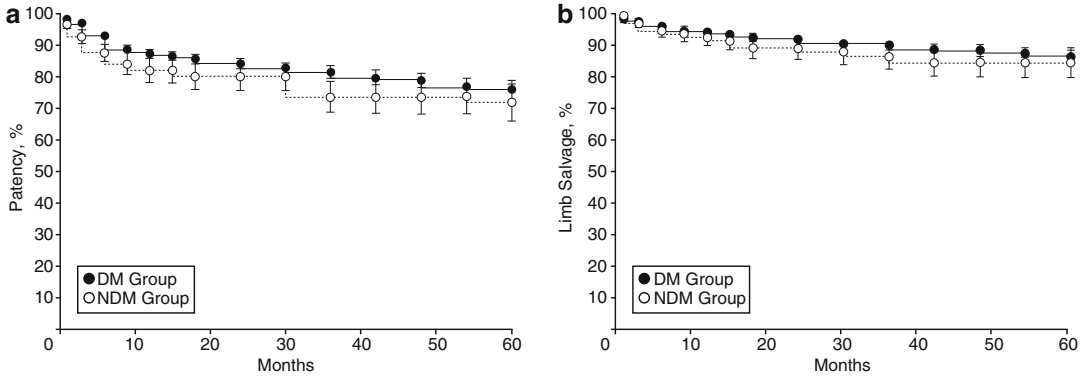

Fig. 19.1 Graft patency (**a**) and limb salvage (**b**) for diabetic and nondiabetic patients undergoing lower extremity bypass and followed for at least 5 years. *From Akbari CM, Pomposelli FB, Jr., Gibbons GW, Campbell DR, Pulling MC, Mydlarz D, LoGerfo FW. Lower extremity revascularization in diabetes: late observations. Arch Surg 2000;135:452–6* (*with permission*)

outcomes in patients undergoing major surgery. Although some studies document increased cardiovascular morbidity in the perioperative period related to major vascular surgery [15], our personal experience suggests that this concept may not necessarily apply to all diabetic patient populations. In our study of 6,565 major vascular procedures of all types, including carotid endarterectomy, aortic aneurysm repair, and lower extremity bypass, diabetes mellitus was not predictive of increased perioperative cardiac morbidity or mortality in logistic regression analysis [20]. In a separate study evaluating outcomes in a patient population undergoing nearly 800 lower extremity bypass procedures with a minimum follow-up of 5 years, the inhospital mortality rate was only 1% and the long-term graft patency, limb salvage, and patient survival rates were comparable to or better than that in nondiabetic patients treated during the same time period [21] (Fig. 19.1). In our opinion, careful perioperative management, including an aggressive approach toward invasive cardiac monitoring in the early postoperative period may contribute to the low cardiac morbidity and mortality rate that we observed in these high-risk patients.

From the vascular surgeon's perspective, the most important difference in lower extremity atherosclerosis in diabetics is the location of atherosclerotic occlusive lesions in the arteries supplying the leg and the foot [8, 10, 22]. In patients without diabetes, typically smokers, atherosclerosis most commonly involves the infrarenal aorta, iliac arteries, and superficial femoral artery with relative sparing of the more distal arteries. In patients with diabetes however, the most significant occlusive lesions typically occur in the infrapopliteal vessels, specifically the anterior tibial, peroneal, and posterior tibial arteries. Arteries of the foot, specifically the dorsalis pedis, tarsal, and plantar arteries, are often spared of disease (Fig. 19.2). This pattern of occlusive disease, known as "tibial artery disease," requires a different approach to vascular reconstruction and presents special challenges for the vascular surgeon. Moreover, diabetic patients who smoke may present with a combination of both patterns of disease, making successful revascularization even more complex.

Patient Presentation and Medical Management

Many patients with diabetes have evidence of peripheral arterial disease manifested by the absence of palpable leg or foot pulses in the presence of minimal or no ischemic symptoms. In these patients, the arterial occlusive disease may be well compensated with the presence of abundant collateral vessels; therefore, no invasive treatment may be necessary. It is crucial to educate such patients about atherosclerotic disease, including its natural history as well as its signs

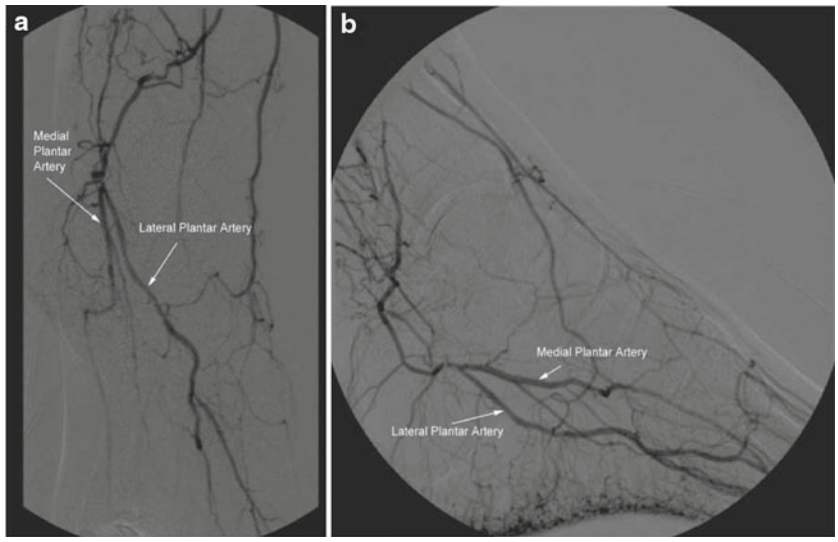

Fig. 19.2 Preoperative antero-posterior (**a**) and lateral (**b**) arteriogram of the foot of a patient undergoing a plantar artery bypass

and symptoms. It is also important to emphasize to the patient that reduction of associated risk factors plays a significant role in disease management, particularly smoking cessation, tight glucose control, and management of dyslipidemia. Regular follow-up clinical examinations, usually at a 6–12 month intervals, are reasonable to track the progression of arterial occlusive disease and its clinical manifestations. Many clinicians will obtain baseline and follow up noninvasive arterial testing, although this is not mandatory. Many such patients have associated coronary and carotid atherosclerosis, which may also be asymptomatic. Routine screening for disease in these territories in the absence of symptoms, purely based on evidence of lower extremity atherosclerosis, may be appropriate in select patients but is probably not cost-effective as a routine in all patients.

Diabetic patients may present with a complex symptom pattern reflecting a combination of ischemic and neuropathic symptoms. The spectrum of symptoms attributable to arterial occlusive disease ranges from asymptomatic to intermittent claudication to ischemic rest pain or more severe symptoms, such as tissue loss or gangrene. Patients with ischemic foot pain at rest, nonhealing foot ulceration or gangrene are considered to have critical or limb-threatening ischemia. Such patients are at imminent risk of limb loss if efforts at revascularization of the extremity are not made. The spectrum of arterial ischemia symptoms does not always follow an orderly progression. Some patients may progress to critical ischemia rapidly without ever noting more mild symptoms of ischemia, such as intermittent claudication. In some patients, ischemic rest pain symptoms may be masked by symptoms of peripheral neuropathy necessitating that the clinician pays careful, detailed attention to the patient's symptom pattern to establish a correct diagnosis and formulate a treatment plan.

Patients presenting with severely disabling intermittent claudication or signs of limb-threatening ischemia, such as ischemic rest pain or tissue loss, may require surgical intervention to correct lower extremity arterial insufficiency. Intermittent claudication usually manifests as pain, cramping or a sensation of severe fatigue in the muscles of the leg, which occurs with walking and is promptly relieved by rest. Claudication symptoms are typically reproducible with similar activities. Many patients adjust their lifestyle to minimize or eliminate any significant walking. The location of discomfort can give hints as to the location of the occlusive arterial disease. Patients with aortoiliac occlusive disease often

complain of buttock and thigh claudication symptoms, while patients with femoral level disease typically report calf discomfort, although patients with aortoiliac occlusive disease can have calf claudication as their only presenting symptom. Patients with tibial arterial occlusive disease may also have calf claudication or may complain of foot discomfort or numbness with walking. Nocturnal muscle cramping is a common complaint among patients with diabetes, but is not a typical symptom of arterial insufficiency even though it may involve the calf muscles. This symptom, therefore, should not be mistaken for intermittent claudication. Most patients with intermittent claudication do not require surgical intervention. Studies on the natural history of claudication have demonstrated that progression to limb threatening ischemia is uncommon [23, 24].

Many patients respond reasonably well to conservative treatment measures for intermittent claudication, such as cessation of tobacco use, correction of risk factors for atherosclerosis, weight reduction when necessary and an exercise program involving walking [25]. Additionally, two medications, pentoxifilline, 400 mg orally three times daily or cilostazol, 100 mg orally twice daily, are approved for the treatment of intermittent claudication due to atherosclerosis [26–28]. Both drugs are generally well tolerated but need to be taken for several weeks before an improvement in walking distance can be appreciated. In the authors' experience, pentoxifilline is rarely effective in relieving claudication symptoms. Although cilostazol has been more effective, side effects including headache and diarrhea are occasionally problematic and this medication is contraindicated in patients with a history of congestive heart failure. A reasonable treatment strategy for intermittent claudication begins with a discussion with the patient about its cause and reassurances that its course is usually benign. The need for smoking cessation, weight loss when appropriate, and life style changes to reduce risk factors are strongly emphasized. Especially, in patients with mild to moderate intermittent claudication symptoms, nonoperative management is the first-line therapy. In addition to risk factor modification, the patient is advised to embark upon an exercise program involving walking. The patient is typically instructed to walk at least 3 or 4 days per week for at least 30 min per session. It is essential for the patient to walk until they reach a point of near-maximal claudication pain before stopping briefly to rest then resume walking. Patients should be advised that a walking program, especially when adhered to for over 6 months, is expected to increase the distance walked before the onset of symptoms and before experiencing maximal pain symptoms [29]. Cilostazol therapy may be instituted to offer symptomatic benefit if walking proves ineffective or if patients cannot or will not exercise. Clopidogrel has also been used for claudication symptoms; however, its efficacy has not yet been proven in clinical trials. Interventions for claudication, including angioplasty or surgery, are reserved for those patients who are severely disabled with a very limited functional capacity, unable to work due to their symptoms, or who have not responded to more conservative treatment. In the authors' experience, patient noncompliance is a common reason for failure of conservative treatment measures. Many patients cannot or will not exercise and others find the degree of improvement with conservative measures inadequate. With the improvement in technology of lower extremity angioplasty and stenting, we tend to offer this less invasive option in patients with lifestyle limiting claudication more readily than we would have previously offered bypass surgery when it was the only available treatment. Nonetheless, in most patients with intermittent claudication, exercise, risk factor reduction, especially the cessation of smoking and the treatment with cilostazol when appropriate should be the first line of therapy.

Most diabetic patients referred for vascular intervention have limb-threatening ischemia, which if not promptly treated is likely to ultimately result in limb amputation. The most common presenting problem is a nonhealing ulcer with or without associated gangrene and infection. Many patients initially develop an ulcer as a result of neuropathy, which will then not heal in spite of proper treatment due to associated arterial insufficiency, the so-called neuroischemic ulcer.

Table 19.1 Distinguishing features of ischemic pain and painful neuropathy

Ischemic rest pain	Neuropathy
Usually unilateral	Often bilateral
Consistently present	Waxes and wanes
Relieved by dependency of foot	Not relieved by dependency
Always associated with absent pulses	Pulses may be present and normal

Some patients are referred after a minor surgical procedure in the foot fails to heal due to ischemia. Patients with limb threatening ischemia can also present with ischemic rest pain with or without associated tissue loss. Ischemic rest pain typically involves the distal foot, particularly the toes. It is exacerbated by recumbency and relieved by dependency. Patients often give a history of noticing pain, numbness, or paresthesias when retiring to bed, which is then relieved at placing their foot in a dependent position. Often the dependent position of the foot is not recognized as the cause of relief and relief may be ascribed to maneuvers, such as walking and stamping, the involved foot on the floor or getting up and taking an oral analgesic medication. It is important but occasionally difficult to differentiate ischemic rest pain from painful diabetic neuropathy, which may also be subjectively worse at night (Table 19.1). Patients with peripheral neuropathy may also present with the absence of ischemic rest pain symptoms in spite of overt severe foot ischemia due to the complete loss of sensation.

Patient Selection

In patients presenting with typical ischemic symptoms mandating treatment, several factors must be taken into consideration when deciding which patients are suitable candidates for arterial reconstruction. Certain patients, such as those who are nonambulatory or bedridden and have no likelihood of successful rehabilitation may not be appropriate candidates for arterial reconstruction. Similarly, patients with severe flexion contractures of the knee or hip are poor candidates for arterial reconstruction. Patients with terminal cancer with very short like expectancy or similarly lethal comorbidities do poorly with vascular reconstruction and are also probably better served by primary amputation. Patients with an unsalvageable foot due to extensive necrosis from infection or ischemia may likewise require primary limb amputation. However, in other patients presenting with infection complicating ischemia, proper control of active, spreading infection should be accomplished prior to arterial reconstruction. Broad-spectrum intravenous antibiotics to cover gram positive, gram negative, and anaerobic organisms should be started immediately after cultures are taken, since many limb threatening infections in diabetic patients are polymicrobial [1, 30]. Once culture data is available, antibiotic coverage can then be appropriately adjusted. In addition, those patients with abscess formation, septic arthritis, or necrotizing fasciitis should undergo prompt incision, drainage, and debridement, including partial open toe, ray, or forefoot amputation as indicated [31] (Fig. 19.3).

In our published series of over 1,000 pedal bypasses, secondary infection was present at the time of presentation in over 50% of patients [32]. Infection places an increased metabolic demand on already ischemic tissues and may accelerate and exacerbate tissue necrosis. Since many diabetic patients have a blunted neurogenic inflammatory response, typical inflammatory signs of infection may be absent or diminished. It is therefore imperative that all ulcers be carefully probed and inspected and superficial eschars be unroofed to look for potential deep-space abscesses which may not be readily apparent on visual inspection of the foot. The need to control spreading infection may delay vascular surgery for several days, but waiting any longer than necessary in an attempt to sterilize foot wounds is inappropriate and may result in further necrosis and tissue loss. Signs of control of spreading infection include reduction of fever and leukocytosis, resolution of cellulitis and lymphangitis, particularly in areas of potential surgical

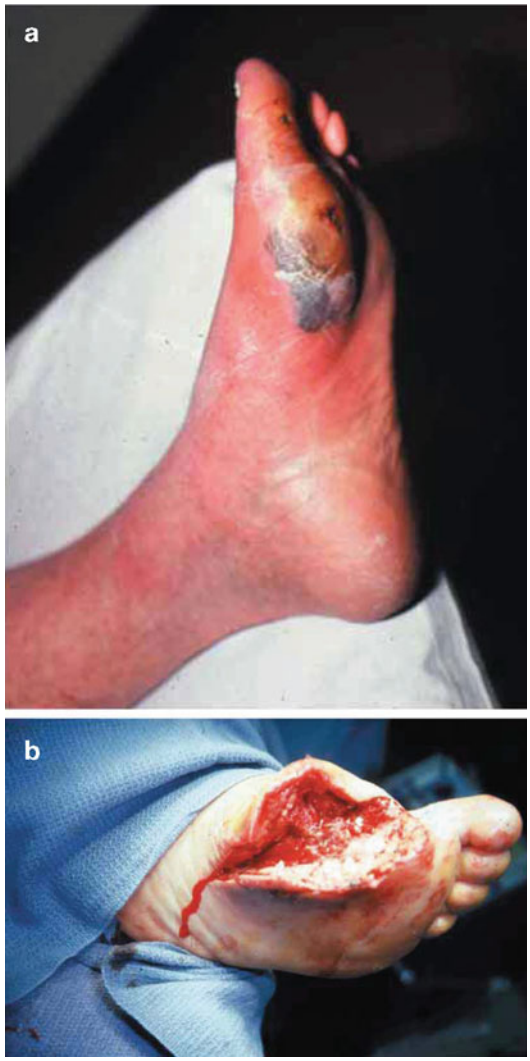

Fig. 19.3 Photographs of the right foot of a patient with diabetes who presented with a rapidly spreading infection as a result of a plantar ulcer over the first metatarsal. (**a**) Marked swelling and erythema of the medial forefoot is evident. There was palpable crepitus and malodorous drainage owing to involvement of the bone, joint, and flexor tendon with gas-forming bacteria. (**b**) Control of this infection required an emergent open first ray amputation. Cultures grew multiple organisms, including *Staphylococcus aureus*, *Proteus,* and anaerobes

incisions, and return of glycemic control, which may be the most sensitive indicator of improvement. During this period which rarely extends beyond several days, duplex imaging, contrast arteriography, and other presurgical evaluations, such as testing for coronary artery disease when necessary can be performed so that revascularization surgery may be undertaken without subsequent delay. In some instances, when endovascular options for revascularization exist, diagnostic arteriography may be followed by endovascular intervention as a means of revascularization in the same setting. In such cases, proceeding with cardiac work-up may not be necessary. One caveat to tissue debridement is that uninfected eschar in the presence of ischemia should not be debrided until arterial reconstruction has been completed. Debriding a dry, uninfected eschar in the presence of severe ischemia will result in extension of necrosis and a larger, deeper ulcer or wound. There are occasional patients in whom infection cannot be totally eradicated prior to revascularization. Patients with severe ischemia may have inadequate blood flow to distal sites to deliver adequate tissue penetration of antibiotics until arterial blood flow has been adequately restored. It is important for these patients to continue antibiotic coverage for several days following arterial reconstructive surgery. Occasionally, patients will seem to have worsening of their infection after revascularization due to the enhanced inflammatory response that occurs once arterial blood flow has been restored. These patients may require one or more subsequent debridements to fully remove all infected and necrotic tissue.

It is important to realize that age alone is not a contraindication to arterial reconstruction. We have successfully performed surgical revascularization procedures in selected patients over the age of 90. When selecting patients for arterial reconstruction, the functional and physiologic status of the patient is far more important than their chronological age. In fact, a limb salvaging arterial reconstruction may mean the difference between continued independent living and the need for permanent custodial nursing home care for the elderly patient. We have evaluated our results with revascularization in a cohort of patients who were 80 years of age or older at the time of arterial reconstruction. In particular, we evaluated the technical success rate of the initial procedure and also two important quality of life outcome measures—the ability to ambulate and

whether or not the patient returned to their own residence following surgery. At 1-year following surgery, the vast majority (>80%) were still ambulatory and residing in their homes either alone or with relatives [33]. These observations emphasize the importance of offering revascularization options to patients regardless of age.

Patients with limb ischemia who present with signs and symptoms of coronary artery disease, such as worsening angina, recent congestive heart failure, or recent myocardial infarction, should undergo efforts to stabilize their cardiac disease prior to arterial bypass surgery. As an alternative, patients with severe symptomatic coronary disease should undergo arteriography with endovascular intervention whenever possible to avoid the potential cardiovascular complications of open surgical revascularization. When bypass surgery is the only possible option, occasionally coronary angioplasty and stenting or even coronary artery bypass grafting may be required prior to lower extremity bypass surgery, although in our experience this has been unusual. For the "typical" patient requiring lower extremity bypass surgery, routine noninvasive cardiac evaluation has been proven to be both costly and unnecessary. Virtually, all diabetic patients with lower extremity ischemia have occult coronary disease [34]. Consequently, screening tests such as dipyridmole–thallium imaging studies are almost always abnormal to some degree. Attempting to quantify the degree of abnormality with such testing has occasionally proved useful in stratifying those patients at excessive risk for perioperative cardiac morbidity or mortality; however, most such patients with severely abnormal scans usually have obvious clinical signs or symptoms as well [35]. As a result, we rely mostly upon the patient's clinical presentation and electrocardiogram in determining when further evaluation is needed and use imaging studies selectively in those patients with unclear or atypical symptoms. In asymptomatic patients who are reasonably active with no acute changes on an electrocardiogram, no further studies are generally undertaken. We have found that several factors have contributed to a significant reduction in perioperative cardiac morbidity and mortality in our patients. These include the frequent use of invasive perioperative cardiac monitoring, such as pulmonary arterial and peripheral arterial catheters, anesthesia management by personnel accustomed to treating patients with ischemic heart disease and postoperative care in a specialized subacute monitored unit with cardiac monitoring capabilities. Moreover, in several prospective randomized trials, the type of anesthesia administered—spinal, epidural, or general endotracheal, did not affect the incidence of perioperative cardiac complications [36] or bypass graft thrombosis [37]. General endotracheal anesthesia remains our preference for most patients.

Patients presenting with limb ischemia in the setting of renal failure present special challenges. When acute renal insufficiency occurs, sometimes as a result of contrast-induced nephropathy after arteriography, surgery should be delayed until renal function stabilizes or returns to baseline. Most such patients will demonstrate a transient rise in serum creatinine in the absence of other symptoms. It is rare that such patients will become anuric or require hemodialysis. Withholding or delaying contrast arteriography in patients with diabetes and compromised renal function is usually unnecessary. If there are extreme concerns about renal function, duplex ultrasound imaging, magnetic resonance angiography (MRA) with time-of-flight imaging and CO_2 angiography are imaging alternatives that can sometimes provide adequate information to plan arterial reconstruction or to allow for more limited and selective contrast arteriography of the tibial and pedal vessels [38].

Patients with chronic, dialysis-dependent renal failure can safely undergo arterial reconstruction. Many such patients have severe, advanced atherosclerosis and have target arteries that are often heavily calcified. Gangrene and tissue loss are frequently present and the healing response in such patients is poor, even with restoration of pulsatile arterial blood flow to the foot. Some such patients will require amputation even with patent arterial bypass grafts. Several studies have demonstrated that while reasonable, graft patency and limb salvage rates in these patients are lower than in patients without chronic renal failure [39–42]. Our own study of 146 patients

with end-stage renal disease undergoing arterial reconstruction for critical limb ischemia demonstrated graft patency and limb salvage rates of 68% and 80%, respectively, at 3 years. Perioperative mortality rate was reasonably low at 3%; however, long-term survival was poor with only 18% or patients alive after 3 years. Other studies have documented higher perioperative mortality rates (9–18%) and lower limb salvage rates (65–70% at 1 year) in this population [43, 44]. Despite this, revascularization still seems to be a reasonable option for end-stage renal failure patients with critical limb ischemia rather than primary amputation in selected patients. The follow-up data available in the literature underscores the importance clinical judgment when considering arterial bypass for limb ischemia in the dialysis patient. Until further studies clarifying the role of bypass surgery in this patient population are available, treatment plans must be individualized with the realization that for some patients, primary amputation may be the best option.

Evaluation and Diagnostic Studies

Noninvasive Testing

The noninvasive vascular laboratory is particularly useful in those diabetic patients presenting with pain in the foot and absent pulses, where the etiology of symptoms is unclear and may be due to either ischemia or painful diabetic neuropathy [45, 46]. Several forms of evaluation with noninvasive testing are helpful in the evaluation of the ischemic foot. Calculation of the ankle-brachial index (ABI) involves determination of bilateral brachial, dorsalis pedis, and posterior tibial artery systolic pressures with the use of a Doppler probe and blood pressure cuff. The highest brachial pressure is used to calculate the ABI on both extremities. The highest foot systolic pressure is used to calculate the ABI for that extremity. An ABI of >1.3 is considered unreliable due to the inability to compress the vessel with the blood pressure cuff due to arterial wall calcinosis. An ABI of 0.9–1.3 is considered in the normal range, whereas a measurement of <0.9 is considered abnormally low. Patients with critical limb ischemia usually have an ABI of less than 0.4. In patients with diabetes, however, care must be taken in interpreting ankle pressures since some patients will have falsely elevated pressures due to calcification of the arterial wall making vessels difficult to compress with a blood pressure cuff [47]. In fact, at least 10% of diabetic patients have incompressible ankle arteries making the ABI incalculable [48]. In patients with normal (0.9–1.3) or low (<0.9) ABIs, toe pressures are not thought to provide any additional information regarding arterial supply to the foot. In patients with elevated ABIs (>1.3), however, toe pressures or calculation of a toe-brachial index (TBI) is thought to provide a more accurate measure of arterial flow to the foot. Toe pressures are determined with the use of a cuff on the toe and either doppler or photoplethysmography measurements distal to the cuff in order to determine a systolic pressure. Whereas 0.9–1.3 is considered a normal ABI, a TBI of >0.6–0.7 is considered normal. An absolute toe pressure of >45–55 mmHg has been demonstrated to have positive predictive value for healing of a foot wound [49].

Pulse volume recordings (PVRs) are also useful in diabetic patients since this measure is unaffected by calcification of the vessels. Severely abnormal PVR waveforms at the ankle or metatarsal level suggest severe ischemia (Fig. 19.4). Some centers have found transcutaneous oxygen measurements [50, 51] to also be useful in these patients. Noninvasive arterial testing with exercise may be helpful in assessing patients with presenting with claudication-like symptoms in the setting of palpable distal pulses [45, 47]. Baseline arterial studies are taken and then repeated after exercise, usually walking on a treadmill at an elevation of 10° until symptoms are reproduced. A subsequent reduction in arterial pressures or worsening of pulse volume waveforms suggests proximal stenotic lesions. Those patients with muscular pain with walking but who have normal waveforms pre- and postexercise may have another etiology of their symptoms, such as spinal stenosis, the so-called pseudoclaudication or neurogenic claudication.

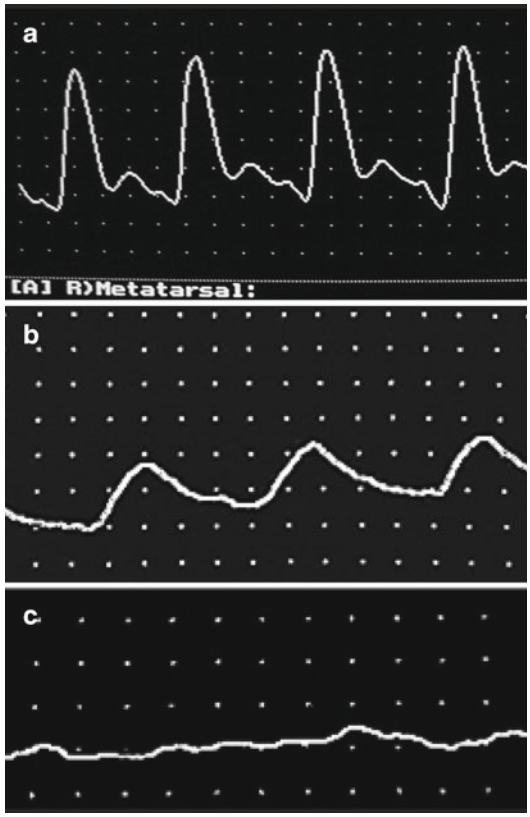

Fig. 19.4 In patients with heavily calcified lower extremity arteries, pulse volume recordings (PVR) can be used as a qualitative assessment of the degree of ischemia based on the appearance of the waveform. For tibial arterial occlusive disease, the tracings at the ankle or forefoot are most important. (**a**) An example of a normal PVR showing a steeply peaked wave with a brisk upstroke, rapid down stroke, and a dicrotic notch. (**b**) A moderately abnormal waveform with blunting and rounding of the waveform and loss of the dicrotic notch. (**c**) Markedly abnormal waveform with flattening of the waveform suggesting severe reduction in arterial flow

Noninvasive testing can also be used to quantify the degree of improvement in arterial circulation following revascularization interventions. Arterial bypasses with vein grafts are susceptible to the development of neointimal hyperplasia, which can lead to stenosis and ultimately graft thrombosis. Ultrasound evaluation of vein grafts with color flow ultrasound scanning is useful in detecting stenoses due to intimal hyperplasia [52]. Duplex surveillance of bypass grafts is performed at 1, 3, 6, 12, 18, and 24 months postoperatively, then every 6–12 months thereafter. When detected, significant stenoses (>50% diameter) can often be repaired by percutaneous balloon angioplasty, vein patch angioplasty, or interposition grafts in order to prevent graft thrombosis [53]. Our preference for the treatment of most typical vein graft stenoses is percutaneous balloon angioplasty. Surgical options are generally reserved for recurrent or longer-segment stenoses.

Noninvasive testing, however, adds little to the evaluation of patients presenting with obvious signs of foot ischemia and absent foot pulses. For most patients, a careful history and physical examination will accurately diagnose significant arterial insufficiency. The most important feature of the physical examination is the status of the foot pulses. If the posterior tibial and dorsalis pedis artery pulses are nonpalpable in patients presenting with typical signs and symptoms of ischemia, no further noninvasive testing is absolutely necessary and contrast arteriography may be performed straight away. Noninvasive testing, when performed prior to percutaneous or surgical revascularization, may be used as a baseline or reference study with which to compare future studies to document and follow improvement in arterial flow.

Invasive Testing

The ultimate goal of lower extremity reconstruction is to restore perfusion pressure in the distal circulation by bypassing all major occlusions and if possible reestablish a palpable foot pulse. The outflow target artery at the location of the distal anastomosis should be relatively free of occlusive disease and demonstrate unimpeded arterial flow into the arteries of the foot. In general, the most proximal artery distal to the occlusion meeting these two criteria is chosen as a bypass target vessel. In order to make these determinations, a comprehensive contrast arteriogram of the entire lower extremity circulation extending from the infrarenal aorta to the base of the toes should be performed. It is crucial to visualize the entire tibial and foot circulation since the former is the

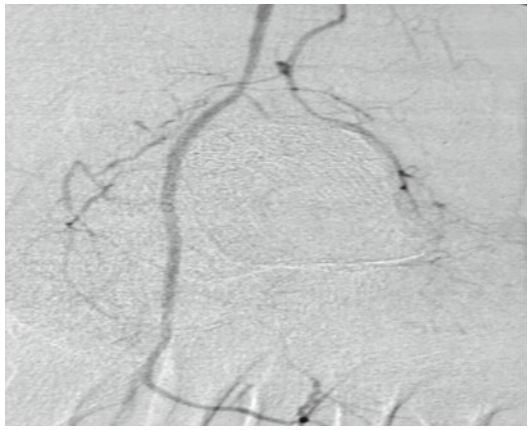

Fig. 19.5 This is an AP view of the foot of the patient seen in Fig. 19.3. The widely patent dorsalis pedis artery is well visualized and can be seen feeding the pedal arch. It is mandatory to obtain a lateral and AP view angiogram of the foot when evaluating the pedal vasculature

most common location of significant occlusive lesions and the latter is an important potential site for the placement of the distal anastomosis of the bypass graft (Fig. 19.5). Iliac artery atherosclerosis accompanies more distal lower extremity disease in approximately 10–20% of patients with diabetes. When encountered and significant (>50% diameter stenosis), balloon angioplasty of iliac lesions with or without placement of a stent, is almost always possible and will improve arterial inflow for bypass. Moreover, this can be performed in the same setting as the diagnostic arteriogram. For many years, our preference has been to exclusively use intra-arterial digital subtraction arteriography to evaluate the lower extremity arterial circulation [54]. With currently available equipment, it is possible to obtain a complete survey from the infrarenal aorta to the base of the toes with less than 100 cc of contrast, about half the amount required for conventional arteriography. Although conventional arteriography can provide excellent views of the lower extremity arterial anatomy, we have found cases where it failed to demonstrate a suitable outflow vessel that was subsequently seen using the digital subtraction method.

As previously discussed, acute renal failure is a concern in diabetic patients undergoing contrast arteriography, especially in those with preexisting renal insufficiency. The most important factor in the prevention of renal failure in these patients has been the use of hydration prior to performing the angiogram [34]. When renal failure does occur, it is almost always reversible, but may delay arterial reconstruction surgery for several days while the creatinine returns to baseline [40]. Arteriography may be performed as a diagnostic or therapeutic study safely even in patients with baseline renal insufficiency by following several basic precautions. First, the patient should be adequately hydrated prior to the procedure. Isoosmolar nonionic contrast, such as iodixanol, should be used when possible, as it has been demonstrated to be associated with a decreased risk of contrast-induced nephropathy in high-risk patients [55]. Contrast dye may be diluted with saline to limit the amount used. Focused studies may be performed when the status of the more proximal vessels are known to be normal by pulse examination and/or noninvasive duplex imaging. *N*-acetylcysteine has been demonstrated in multiple studies to decrease the risk of contrast-induced nephropathy [56, 57]. Premedication with *N*-acetylcysteine is typically administered as an oral solution 600 mg twice a day the day before and the day of the procedure for a total of four doses. Intravenous hydration with a sodium bicarbonate solution has been demonstrated to reduce the incidence of contrast induced nephropathy as well [58, 59].

Thus when appropriately treated, arteriography should not be withheld due to fear of exacerbating moderate chronic renal insufficiency. When renal function does worsen, it is usually asymptomatic and transient with creatinine levels usually returning to normal within a few days. For patients with more severe renal dysfunction, MRA can provide adequate images of the distal circulation to plan an arterial reconstruction. Although some centers feel that this technique is superior to contrast arteriography [38], we have found that intra-arterial digital subtraction arteriography continues to provide the best quality images; therefore, we reserve MRA for those patients in which the administration of contrast is potentially harmful or absolutely contraindicated. We have published a more extensive description

of the arterial imaging techniques recommended for patients with lower extremity ischemia and diabetes elsewhere [60].

Vascular Reconstruction

Once the patient with an ischemic extremity has undergone the appropriate imaging evaluation, a decision can be made regarding the most suitable revascularization technique. This includes the possibility of endovascular or surgical intervention, or sometimes a combination of both approaches. When evaluating the most appropriate revascularization plan for any given patient, particular attention should be paid to establishing in-line flow to the foot. In general, short stenoses or occlusions may be more likely than longer lesions to be successfully addressed by endovascular means, such as balloon angioplasty and/or stenting. Many factors play a role in determining if a particular occlusive lesion would be best treated by angioplasty, stenting, other endovascular techniques, or with open surgical options. The main types of open surgical options for revascularization of infrainguinal disease include endarterectomy, patch angioplasty, and bypass grafting. Factors, such as the patient's overall comorbidities, availability of native bypass conduit, occlusive lesion characteristics, and severity of ischemia, all contribute to the formulation of the most appropriate revascularization plan for the patient.

Endovascular Therapy

Endoluminal intervention has gained widespread use in patients with critical limb ischemia when the anatomy of the lesion deems this option appropriate. In the past, endovascular treatment was mostly limited to angioplasty and stenting of larger vessels, such as the iliac arteries to improve arterial inflow in preparation for a more distal bypass. Endovascular intervention has become a reasonable option to consider, especially in the patient with contraindications to surgical revascularization, such as significant comorbidities or paucity of vein conduit for bypass. The development of lower profile, smaller diameter balloons, stents, and steerable guidewires has made infrainguinal and even tibial and pedal angioplasty feasible with a high likelihood of technical success. Several authors have reported remarkably good immediate and short-term results of tibial angioplasty, although most reports contain a heterogeneous patient population with small numbers of patients. In one of our reported series, technical success was achieved in 90% of tibial angioplasty cases and limb salvage at 1 year was >80% [61]. The likelihood of technical success is dependent upon the severity of the occlusive lesions. In our published series of infrapopliteal angioplasty in 176 limbs with critical ischemia, technical success was 93% overall and was noted to be related to lesion length. Technical success was 100% for short, focal stenoses (1–4 cm) or occlusions (<2 cm) but decreased to 75% for longer occlusions (>2 cm) or diffusely diseased arteries. Patency at 1 year was only 39% but limb salvage was 84% [62]. In one retrospective analysis of the use of tibial angioplasty in patients with critical limb ischemia who were not felt to be candidates for surgical revascularization due to the absence of conduit or prohibitive comorbidities, technical success was 96% for lesions ranging from 3 to 25 cm [63].

Another randomized, multicenter, prospective trial compared angioplasty to bypass for critical limb ischemia due to infrainguinal arterial occlusive disease. At 2-year follow-up, mortality, limb salvage and survival was identical for the two groups. Although the cost of bypass was higher, the angioplasty group required reintervention more frequently. Surprisingly, functional outcomes and quality of life measures were identical for both groups [64]. In a post hoc analysis of patients surviving beyond 2 years, limb salvage and survival were higher for patients undergoing bypass. In spite of its shortcomings, this study validated the use of tibial angioplasty for critical limb ischemia especially for those patients with strong contraindications to surgery or anesthesia and with an anticipated life expectancy of less than 2 years. In one recent series of 111 patients

undergoing tibial level endovascular intervention for limb salvage, diabetes had no effect on outcome. In this group, similar to in other studies the 1-year reintervention rate was high at 50% [65]. For healthier patients with available conduit, primary bypass remains the best option due to less need for reintervention, and better long-term limb salvage and survival.

Surgical Revascularization

Vein bypass grafts for critical lower extremity ischemia are considered the gold standard based on their safety and efficacy. Perioperative mortality in most contemporary series ranges from 1 to 5% [66] and limb salvage approaches 90% at 5 years for many patients [32]. Although these results are excellent, they do not reflect the high cost of recovery for many patients to achieve this outcome. Surgical wound morbidity is common ranging from 10 to 50% [67, 68]. Limb swelling, delayed healing of ischemic wounds and the need for additional procedures may delay full recovery for many months. Early graft thrombosis, while uncommon, may result in amputation even with subsequent attempts to salvage the graft. For patients with inadequate greater saphenous vein who require alternative vein conduits, bypass procedures are technically more laborious and have worse outcomes. In our study evaluating quality of life measures in patients undergoing arterial bypass for limb salvage, less than 50% reported feeling they were back to normal 6 months after surgery [69]. In a similar study, only 15% of patients achieved the ideal outcome of a patent graft with no need for revision, no wound complications and a healed foot following bypass. These observations are especially sobering when considering the fact that 50% of patients survive less than 5 years after their limb salvage procedure [70]. Regardless, outcomes after surgical revascularization are superior to those seen with primary amputation or endovascular management for patients with a suitable inflow and outflow target vessel and conduit who are felt to be reasonable operative candidates.

Conduit

One of the most important developments in vascular surgery has been the demonstration that autogenous saphenous vein as opposed to prosthetic graft material gives the best short- and long-term results for distal bypass. In a large multicenter prospective randomized clinical trial, 6-year patency of saphenous vein grafts was more than four times higher than that of prosthetic grafts [71]. For over six decades, the standard procedure performed for lower extremity arterial revascularization has been the reversed saphenous vein bypass [72]. An inherent problem with reversing the vein, which is necessary to overcome the impediment of flow from intact venous valves, is the size discrepancy that results between the arteries and veins when anastomoses are performed. Vein grafts that have the diameter of less than 4 mm at the distal end can thrombose when connected directly to the much larger common femoral artery given the size discrepancy. For many years, some vascular surgeons routinely discarded saphenous veins that were smaller than 4 mm at the distal end in order to prevent this cause of early graft thrombosis when performing arterial bypass with reversed saphenous vein. Methods were developed to render the valves incompetent in order to allow the vein to be used in nonreversed or "in-situ" manners. However, no procedure was widely accepted until the late 1970s when Leather and associates described a new technique using a modified Mills valvulotome which cut the valves atraumatically [73]. Vascular surgeons enthusiastically embraced the Leather technique and began reporting improved results with the in-situ bypass [74–76]. This led some to conclude that the in-situ bypass possesses some inherent biologic superiority to the reversed saphenous vain graft [77]. However, evidence to support this concept is lacking [78]. Moreover, when in-situ bypasses are compared to more contemporary series of reversed saphenous vein bypasses, no apparent superiority is evident [79]. In our own experience, we have frequently used both procedures and have observed essentially identical results with both vein configurations [80]. Nevertheless, the in-situ

technique is an important advancement in lower extremity reconstructive surgery and continues to be used widely by many vascular surgeons.

In the 1980s, Ascer and associates [81] reported the first series of bypass grafts with inflow taken from the popliteal artery. They showed equivalent results with the traditional approach of taking inflow from the common femoral artery. These results have been confirmed by other groups including our own and this technique has proven to be another important advancement in arterial reconstruction in patients with diabetes [82, 83]. Because atherosclerotic occlusive disease often spares the superficial femoral artery in diabetics, the popliteal artery can be readily used as a source of inflow for the bypass graft. Doing so shortens the operative procedure time, shortens the length of the bypass and avoids potentially troublesome groin wound complications, which often accompany thigh and groin dissections. Short vein grafts are also advantageous in patients who have a limited quantity of adequate saphenous vein. Our experience with extreme distal arterial reconstructions has shown that popliteal artery inflow is possible in about 60% of diabetic patients undergoing vascular reconstruction in the lower extremity [80].

Patients requiring surgical bypass revascularization should undergo bilateral lower extremity venous mapping. This entails duplex ultrasound evaluation of the great and small saphenous veins and provides such details as patency, diameter, and the presence of wall thickening or intraluminal webs or thrombus. When leg vein is not available or is not suitable, arm vein mapping should be performed in search of a cephalic or basilic vein conduit for use. Our preference is that the vein, whether saphenous or other, be larger than 2 mm in diameter and free of evidence of wall thickening. Vein mapping is typically performed with a gentle tourniquet placed on the proximal aspect of the extremity to dilate the vein distally. Ipsilateral greater saphenous vein is the conduit of choice for infrainguinal leg bypass. When the ipsilateral saphenous vein is unavailable secondary to previous harvesting or stripping, alternative sources of conduit must be used. Although some surgeons use a prosthetic graft in these circumstances, alternative vein grafts, including contralateral great saphenous vein, arm vein, or small saphenous vein, can be used. In patients with an absent ipsilateral great saphenous vein, the likelihood of requiring another arterial reconstruction in the opposite extremity approaches 40% at 3 years following the first operation [84]. Because of this, some surgeons hesitate to harvest the contralateral saphenous vein, although at times it is the only option for conduit for the presently threatened limb. Some patients undergoing evaluation for lower extremity revascularization do not have any adequate available saphenous vein due to its use for other vascular procedures or removal for venous insufficiency. When saphenous vein is unavailable bilaterally, our vein conduit of choice is cephalic or basilic vein. Our results with arm vein grafts have been improved by examining the vein with an angioscope intraoperatively to exclude segments with strictures or recanalization from trauma induced by previous venipuncture or thrombosis [85]. Using the angioscope in this way to evaluate the quality of arm vein conduit has significantly improved our results with these grafts and further reduces the number of patients requiring the use of prosthetic conduit [86]. Although arm vein is a reasonable conduit in most patients, we hesitate to harvest arm vein for leg bypass in patients with end-stage renal disease given the need for arm vein in performing the most optimal arteriovenous access surgery. One potential disadvantage of arm vein conduits is their limited length. The use of popliteal artery inflow makes the use of shorter arm vein grafts possible in many patients. Moreover, the use of composite grafts made of various segments of arm vein, including the cephalic-basilic vein loop graft [87], can provide enough conduit length to reach from the groin to the distal tibial and even foot vessels in many patients. Our results with arm vein grafts in over 500 procedures have been reported [88]. Patency was 57.5% and limb salvage was 71.5% at 5 years. These results were inferior to those with de novo reconstructions done with saphenous vein, however, significantly better than those reported with prosthetic conduits. A recent report on the outcomes of tibial bypass with prosthetic graft, heparin bonded polyfluorotetraethylene (ePTFE), versus saphenous vein conduit noted a significant improvement in patency rates

associated with saphenous vein use. Patency of the graft was 75% with ePTFE versus 86% with saphenous vein graft during the follow-up period which ranged from 1 to 12 months [89]. This demonstrates the patency advantage of using saphenous vein when available despite the advances in prosthetic graft construction.

Bypass Anatomy

A review of arteriograms at our institution imaging the entire lower extremity circulation in patients evaluated for revascularization demonstrated that in 10% of cases a foot vessel, usually the dorsalis pedis artery is the only suitable outflow. In another 15% of patients, the dorsalis pedis artery appears to be a better quality outflow target vessel than other patent but diseased tibial vessels. As a result, we began performing bypasses to the dorsalis pedis artery in situations where no other bypass option existed and where we felt the patient was facing amputation as the only alternative. Early results proved gratifying enough that we standardized our technique and indications to encompass all patients where we thought the dorsalis pedis artery was the best bypass option even if more proximal outflow target arteries were present [90]. Our experience with vein bypass grafts to the dorsalis pedis artery exceeds 1,000 procedures with follow up extending beyond 10 years. At 5 years, graft patency was 63% and limb salvage was 78%; however, patient survival was less than 50% [91]. Approximately 60% of patients requiring pedal bypass present with some degree of foot infection, raising concerns about placing an arterial graft in such close proximity to an infection. This has not proved hazardous provided that active, spreading sepsis is controlled prior to surgery [5]. Our results have compared favorably with other reports of pedal level arterial reconstruction [92–96] and are comparable to or better than results now routinely reported for popliteal and tibial artery reconstructions. In advanced cases of distal ischemia, or in cases of failed pedal bypass, patients may have no available outflow vessel other than the lateral tarsal branch of the dorsalis pedis artery or the lateral or medial plantar branches of the posterior tibial artery. In our series of 98 tarsal and plantar bypasses, 30-day mortality was 1% and early graft failure, within 30 days, occurred in 11%. In this group, secondary graft patency was 70% at 1 year and 50% at 5 years. Limb salvage was nearly 70% at 5 years [97]. These results are encouraging in our efforts at limb salvage in a group of patients that are all too often advised that limb amputation is the only option by physicians who do not consider extreme distal bypass as a treatment option (Fig. 19.6). Distal arterial reconstructions present special technical challenges for the vascular surgeon and require meticulous attention to detail. The target arteries are usually small, 1.0–2.0 mm in diameter, and often calcified due to medial calcinosis.

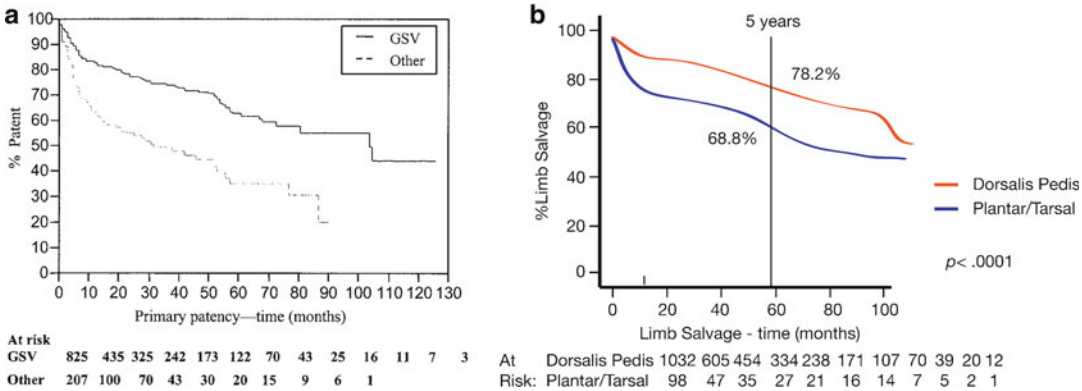

Fig. 19.6 Primary patency (**a**) and limb salvage (**b**) for patients undergoing bypasses to the dorsalis pedis artery and to the plantar/tarsal arteries

Since long-term success of distal bypass requires the use of venous conduit, harvesting an adequate venous conduit is essential and can often present problems, particularly when the ipsilateral saphenous vein is not available. Technical improvements in arteriography, surgical instruments and sutures and techniques such as in-situ bypass have significantly improved the outcome of distal arterial bypass, and outstanding results are often reported in contemporary series. These improvements have proved to be especially beneficial to patients with diabetes mellitus, since their occlusive disease almost always requires a bypass to this level. In particular, the development and application of bypasses to the dorsalis pedis artery has had a direct effect on our own experience in the likelihood of amputation in patients with diabetes presenting with limb threatening ischemia. Since its inception, pedal bypass has resulted in a significant decline in all amputations performed for ischemia [98]. Currently, bypasses to the dorsalis pedis artery constitute approximately 20% of all lower extremity arterial reconstructions in our patients with diabetes.

It is important to remember, however, that foot artery bypass is not the only procedure applicable to patients with diabetes. In general, the goal of treatment is to restore maximal arterial flow to the foot since this provides the best chance for healing. The preoperative diagnostic arteriogram is the key piece of information necessary in planning the appropriate surgical procedure for each patient. If a bypass to the popliteal or tibial artery restores maximal arterial flow and restoration of palpable foot pulses, bypasses need not extend to the level of the foot. Since the quality of the venous conduit is the most important determinant in long-term success using the shortest length of high quality venous conduit necessary to achieve this goal is the basic rule. Each operation must be individualized based on the patient's available venous conduit and arterial anatomy as demonstrated on the preoperative arteriogram. In addition, with the advances in endovascular technology, patients should be assessed during the diagnostic arteriogram for endovascular options as well.

Arterial Bypass in Type 1 Diabetics and Young Patients

Young patients with juvenile onset type 1 diabetes mellitus may develop ischemic foot complications from premature atherosclerosis. In contradistinction to older patients, atherosclerosis in this group is rapidly progressive and associated with a worse prognosis [1, 4–10]. Younger patients undergoing revascularization have been found to be at increased risk for perioperative complications, have an increased rate of multiple revascularization procedures and have more frequent progression to extremity amputation. We reviewed all patients under 40 years old undergoing infrainguinal revascularization at our institution from 1990 to 2000 [99]. Fifty-one patients undergoing 76 lower extremity revascularizations were identified. Type 1 diabetes mellitus was very prevalent, afflicting over 94% of patients. During the follow-up period, 11.8% of patients required additional ipsilateral revascularization, 31.3% required a contralateral bypass graft and in 23.5% major amputation was ultimately necessary. The success rate for secondary procedures was marginal when compared to the primary procedures. The primary patency rate, secondary patency rate, and limb salvage rates were 66.7%, 62.5%, 77.8%, respectively, at 1 year and 44.4%, 41.7%, and 64.8%, respectively, at 5 years. Long-term survival was 75% at 5 years. The results are inferior to those of our older patients where graft patency and limb salvage approach 80% and 90% at 5 years. The worse outcomes may be due to a more aggressive and rapidly progressive form of atherosclerosis or may be a consequence of the relatively high incidence of dialysis-dependent renal failure in these patients. Like patients on chronic hemodialysis, the observed results are inferior to more "typical" patients and attempts to salvage failed reconstructions were rarely successful. These facts must be discussed frankly with the patient prior to initiating therapy and treatment should be individualized based on the clinical situation with the realization that for some patients, amputation may be the best first treatment.

Perioperative Medical Management

Intensive medical therapy and control of diabetes may result in lower rates of infection and other serious perioperative complications. In a prospective randomized, controlled study of surgical intensive care unit patients who were receiving mechanical ventilation, investigation of the effects of intensive insulin therapy was performed and reported [100]. The treatment group received intensive insulin therapy maintaining a blood glucose level between 80 and 110 mg per deciliter. A total of 1,548 patients were enrolled and at 12 months the mortality during intensive care was reduced from 8% in the control group to 4.6% ($p=0.04$) in the treatment group. This effect was most dramatic in patients who remained in the ICU for longer than 5 days (20% control group versus 11% for intensive therapy; $p=0.005$). The beneficial effects were also seen in reduction of infection and sepsis, renal failure requiring dialysis and ICU stay. Although the use of this intensive insulin protocol has not been studied in patients outside of the intensive care unit, it is likely that a similar clinical effect would be seen in diabetic patients undergoing lower extremity arterial reconstructions, where the incidence of wound infection can be as high as 40%.

In addition to maintaining very strict glucose control, our perioperative management plan includes several other important measures designed to decrease cardiac and neurovascular complications and improve early graft patency. In the absence of contraindications, all patients if not currently taking are started on a statin, aspirin, and a β-blocker. Statin dosing is generally optimized as an outpatient and its use is associated with improved patency of autogenous infrainguinal bypass grafts [101]. Aspirin is given as 325 mg daily unless the patient is taking other anticoagulants in which case the dose is reduced to 81 mg daily. Recent evidence supports the use of clopidogrel in addition to aspirin to decrease rates of graft occlusion, amputation, and death specifically in patients undergoing bypass to below-knee targets with prosthetic conduit [102]. This study was designed as a placebo-controlled trial and documented a 35% risk reduction in graft occlusion, need for amputation, and death in patients with prosthetic below-knee bypass, but no such advantage in patients undergoing vein bypass. In addition, the CAPRIE trial demonstrated benefit to administering clopidogrel in addition to aspirin to patients with atherosclerosis in reducing the combined risk of ischemic stroke, myocardial infarction or vascular death [103]. Subcutaneous unfractionated heparin is administered every 8 h postoperatively until discharge for venous thromboembolism prophylaxis unless the patient is on therapeutic anticoagulation already. β-blockers are initiated preoperatively with a goal to reduce heart rates to less than 70 preoperatively and less than 80 postoperatively. There is recent evidence showing that the initiation of preoperative β-blockers at least a week before vascular surgical procedures is associated with reduced 30-day cardiac events and long-term mortality, whereas starting them within a week of surgery does not seem to provide the same benefit [104]. In our practice, serum hematocrit is kept greater than 26%. Intravenous fluid replacement is limited and fluid overload is rapidly treated with intravenous diuretics. Patients are transferred to a special monitored nursing "step-down" unit for 48 h after surgery. This unit can accept patients with pulmonary artery catheters and radial arterial lines which are used liberally especially in patients with known uncorrected ischemic cardiovascular disease, a history of congestive heart failure, depressed myocardial function, or chronic renal failure.

The importance of aggressive medical management of the diabetic patient undergoing revascularization for the treatment of critical limb ischemia cannot be emphasized enough. We believe that attention paid to these issues plays a vital role in minimizing perioperative complications in a patient population with multiple comorbidities.

Management of Foot Wounds

Successful arterial reconstruction with restoration of maximal arterial flow does not end our responsibility to the patient. Often, significant wounds or ulcerations may still be present on the foot and require meticulous management. Devising an appropriate treatment plan to close the wounds and heal the foot is the ultimate goal. Until the skin envelope is intact, the patient is still susceptible to infection even with excellent arterial circulation. The methods involved in healing open wounds and ulcerations in the diabetic foot after restoration of arterial flow are complex and extend beyond the scope of this chapter. A variety of treatment methods are used and are individualized according to the patient's clinical circumstances. While many small ulcers can be left to heal by secondary intention, some may require toe or partial forefoot amputation especially when associated with gangrene or chronic osteomyelitis. For larger wounds, split thickness skin grafts may be used when the area involved is non-weight bearing. For patients with complex wounds of the weight bearing surfaces, particularly the heel, or when bone or tendons need to be covered, more sophisticated plastic surgical reconstructions involving local rotational flaps and even free tissue transfers have been occasionally employed in our practice. Proper application of these procedures requires the expertise of plastic surgeons in conjunction with foot and ankle or podiatric surgeons to be successfully carried out.

Conclusion

This chapter has reviewed the principles of evaluation, diagnosis, and treatment of arterial disease in the diabetic patient with lower extremity ischemia (Fig. 19.7). Rejection of the small vessel hypothesis coupled with an understanding of the unique pattern of atherosclerotic occlusive disease in the lower extremity of patients with diabetes is essential to providing proper treatment. Recognizing the interplay of neuropathy and infection with ischemia and providing appropriate treatment for them as well as addressing arterial insufficiency is essential to ultimate success in limb salvage. A thorough understanding of the pathophysiology of ischemia and a carefully planned approach, including the prompt control of infection when present, high quality digital subtraction arteriography, and distal arterial reconstruction, whether by surgical or endovascular means to maximize foot perfusion should lead to limb salvage rates in patients with diabetes which equal or exceed that achieved in nondiabetic patients with lower extremity ischemia.

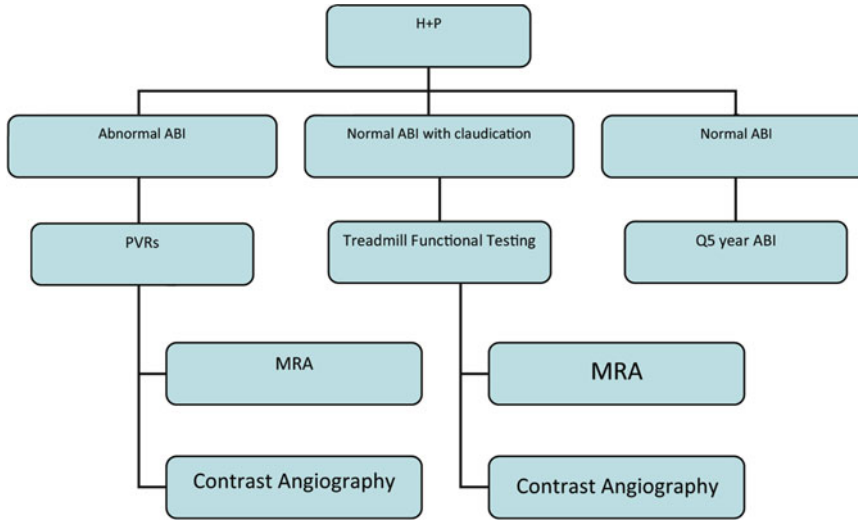

Fig. 19.7 Algorithm for assessing peripheral vascular disease in the diabetic patient (based on recommendations laid out in the 2003 ADA Consensus Statement [Peripheral Arterial Disease in People with Diabetes, American Diabetes Association Consensus Statement, *Diabetes Care*, 26(12):3333–3341, Dec 2003])

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Charcot Arthropathy in the Diabetic Foot

20

Robert G. Frykberg and Lee C. Rogers

Abstract

The Charcot foot is a devastating but oftentimes preventable complication of diabetes with peripheral neuropathy. The condition has several synonyms including Charcot's arthropathy, Charcot joint disease, Charcot syndrome, tabetic arthropathy, diabetic neuropathic osteoarthropathy, and many derivations or combinations thereof. It is named after Jean-Martin Charcot (1825–1893), a French neurologist who first described the joint disease associated with tabes dorsalis and named it the "arthropathy of locomotor ataxia." In 1881, J-M Charcot presented his findings at the 7th International Medical Congress in London which was attended by many acclaimed physicians of the era. During this meeting the eponym "Charcot's Disease" was designated by Sir James Paget to these degenerative neuropathic changes in bones and joints. Although W. Musgrave in 1703 and later J.K. Mitchell in 1831 ostensibly described osteoarthropathy associated with venereal disease and spinal cord lesions, respectively, Charcot's name remains synonymous with neuropathic arthropathies regardless of etiology.

Keywords

Etiology • Charcot arthropathy • Radiographic findings • Forefoot • Tarsometatarsal (Lisfranc's) joint • Midtarsal • Naviculocuneiform joints • Ankle • Subtalar joint • Calcaneal insufficiency avulsion fracture • Acute Charcot arthropathy • Conservative management • Surgical therapy

Introduction

The Charcot foot is a devastating but oftentimes preventable complication of diabetes with peripheral neuropathy. The condition has several synonyms including Charcot's arthropathy, Charcot joint disease, Charcot syndrome, tabetic arthropathy, diabetic neuropathic osteoarthropathy, and many derivations or combinations thereof. It is

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named after Jean-Martin Charcot (1825–1893), a French neurologist who first described the joint disease associated with tabes dorsalis and named it the "arthropathy of locomotor ataxia." In 1881, J-M Charcot presented his findings at the 7th International Medical Congress in London which was attended by many acclaimed physicians of the era. During this meeting the eponym "Charcot's Disease" was designated by Sir James Paget to these degenerative neuropathic changes in bones and joints [1, 2]. Although W. Musgrave in 1703 and later J.K. Mitchell in 1831 ostensibly described osteoarthropathy associated with venereal disease and spinal cord lesions, respectively, Charcot's name remains synonymous with neuropathic arthropathies regardless of etiology [2–5].

W.R. Jordan in 1936 was the first to fully recognize and report on the association of neuropathic arthropathy with diabetes mellitus [6]. In that rather comprehensive review of the neuritic manifestations of diabetes, he described a 56-year-old woman with diabetes duration of approximately 14 years who presented with "a rather typical, painless Charcot joint of the ankle." His description typifies the classic presentation we now commonly recognize in patients with long standing diabetes and neuropathy. Subsequently, Bailey and Root in their 1947 series noted that 1 in 1,100 patients with diabetes mellitus developed neurogenic osteoarthropathy [7]. In the classic 1972 Joslin Clinic review of 68,000 patients by Sinha et al., 101 patients were encountered with diabetic Charcot feet [8]. This ratio of 1 case in 680 patients with diabetes brought greater attention to this disorder and characterized the affected patients' clinical and radiographic presentations. In the subsequent 30 years, there has been a significant increase in the number of reports on diabetic osteoarthropathy, its complications, and management [6–10]. The prevalence of this condition is highly variable, ranging from 0.15% of all diabetic patients to as high as 29% in a population of only neuropathic diabetic subjects [2, 8, 10, 11]. A prospective study of a large group of diabetic patients from Texas reported an incidence of 8.5 per thousand per year. Neuroarthropathy was significantly more common in Caucasians than in Mexican Americans (11.7/1,000 vs. 6.4/1,000) [12]. While this study may give us better insight into the true frequency of osteoarthropathy in diabetes, much of the data we currently rely upon is based upon retrospective studies of small single center cohorts. Nonetheless, the incidence of Charcot cases reported is very likely an underestimation since many cases go undetected, especially in the early states [2, 11, 13]. The frequency of diagnosis of the diabetic Charcot foot appears to be increasing as a result of increased awareness of its signs and symptoms [14]. Although the original descriptions of neuropathic osteoarthropathy were attributed to patients with tertiary syphilis, diabetes mellitus has now become the disease most often associated with this severe foot disorder. Not only are diabetic patients with Charcot foot deformities at greater risk of amputation than those with neuropathic ulcers without osteoarthropathy but a study from the UK has also found them to have a higher mortality [15]. While the power of this study did not allow for significant differences to emerge, it does confirm the need for larger population based studies to fully elucidate the epidemiology of this limb-threatening complication. Overall, the 4 or 5 year relative mortality rate is 28–45% in those with Charcot foot and diabetes [15, 16]. van Baal reported the life expectancy of someone diagnosed with Charcot foot is 7.9 years in the UK [17].

Etiology

Charcot foot (neuropathic osteoarthropathy) can be defined as a noninfectious and progressive condition of single or multiple joints characterized by joint dislocation, pathologic fractures, and severe destruction of the pedal architecture which is closely associated with peripheral neuropathy [2, 9]. Almost uniformly, trauma of some degree when superimposed on the neuropathic extremity precipitates the cascade of events leading to the joint destruction. Osteoarthropathy, therefore, may result in debilitating deformity with subsequent ulceration and even amputation [4, 13]. Neuroarthropathy can result from various

Table 20.1 Diseases with potential for causing neuropathic osteoarthropathy

Disorder	Predilection site
Diabetes mellitus	Foot and ankle
Tabes Dorsalis	Knee, shoulder, hip, ankle, spine
Syringomyelia	Shoulder, elbow, cervical spine
Leprosy (Hansen's disease)	Foot, ankle, hand
Spina bifida	Hip and knee
Meningomyelocele	Foot and ankle
Congenital insensitivity to pain	Ankle and foot
Chronic alcoholism	Foot
Peripheral nerve injury	Ankle and knee
Sciatic nerve severance	Ankle and knee
Spinal cord injury	Varies with level of injury
Hysterical insensitivity to pain	Variable
Myelodysplasia	Variable
Multiple sclerosis	Variable
Riley–Day syndrome	Variable
Intra-articular injections	Variable
Paraplegia	Variable

disorders which have the potential to cause a peripheral neuropathy. With the decline in numbers of patients with tertiary syphilis since Charcot's time and the concomitant rise in prevalence of diabetes mellitus, the latter disease has now become the primary condition associated with Charcot joints. Table 20.1 lists the various neuropathic disorders which can compromise joint mechanisms including their predilection for sites of involvement [2, 8, 9].

There are several conditions producing radiographic changes similar to Charcot joints. These include acute arthritides, psoriatic arthritis, osteoarthritis, osteomyelitis, osseous tumors, and gout. These joint affectations in the presence of neuropathy make the correct diagnosis even more difficult to ascertain [8]. Nonetheless, the characteristics of the joint changes, site for predilection, and clinical correlation assist in determining the true underlying diagnosis.

The primary risk factors for this potentially limb threatening deformity are the presence of dense peripheral neuropathy, normal circulation and a history of preceding trauma, often minor in nature [4, 18]. There is no apparent predilection for either sex [2]. Trauma is not necessarily limited to typical injuries such as sprains, contusions, or fractures. Foot deformities, prior amputations, joint infections, or surgical trauma may result in sufficient stress that can lead to Charcot joint disease. Other factors possibly implicated in the etiology of osteoarthropathy are metabolic abnormalities, renal transplantation, immunosuppressive/steroid therapy, impaired cartilage growth, and nonenzymatic glycosylation [2].

Although the exact pathogenesis may vary from patient to patient, it is undoubtedly multifactorial in nature [2, 18, 19]. The *neurotraumatic* (German) theory has traditionally been proposed as the primary etiology of osteoarthropathy in which neuropathy and repeated trauma produce eventual joint destruction. The loss or diminution of protective sensation allows repetitive micro- or macrotrauma producing intracapsular effusions, ligamentous laxity, and joint instability. With continued use of the injured extremity further degeneration ensues that eventually results in a Charcot joint. Underlying sensory neuropathy resulting from any disorder is therefore a prerequisite under this theory of pathogenesis. However, the neurotraumatic theory does not explain all accounts of Charcot arthropathy, especially its occurrence in bedridden patients [2, 4, 9].

The *neurovascular reflex* (French) theory, in contrast, proposes that increased peripheral blood flow due to autonomic neuropathy leads to hyperemic bone resorption [20]. This theory might indeed correspond to Charcot's original hypothesis of a central "nutritional" defect, although we now recognize this process as a *peripheral* nerve disorder. Autonomic neuropathy (and endothelial dysfunction) results in an impairment of vascular smooth muscle tone and consequently produces a vasodilatory condition in the small arteries of the distal extremities [21, 22]. Impairment of neurogenic vascular responses in patients with diabetic neuropathy has been supported by one study that consequently also showed preserved maximal hyperemic responses to skin heating in patients with Charcot arthropathy [23]. In concert with associated arteriovenous shunting, there is a demonstrable increase in bone blood flow in the

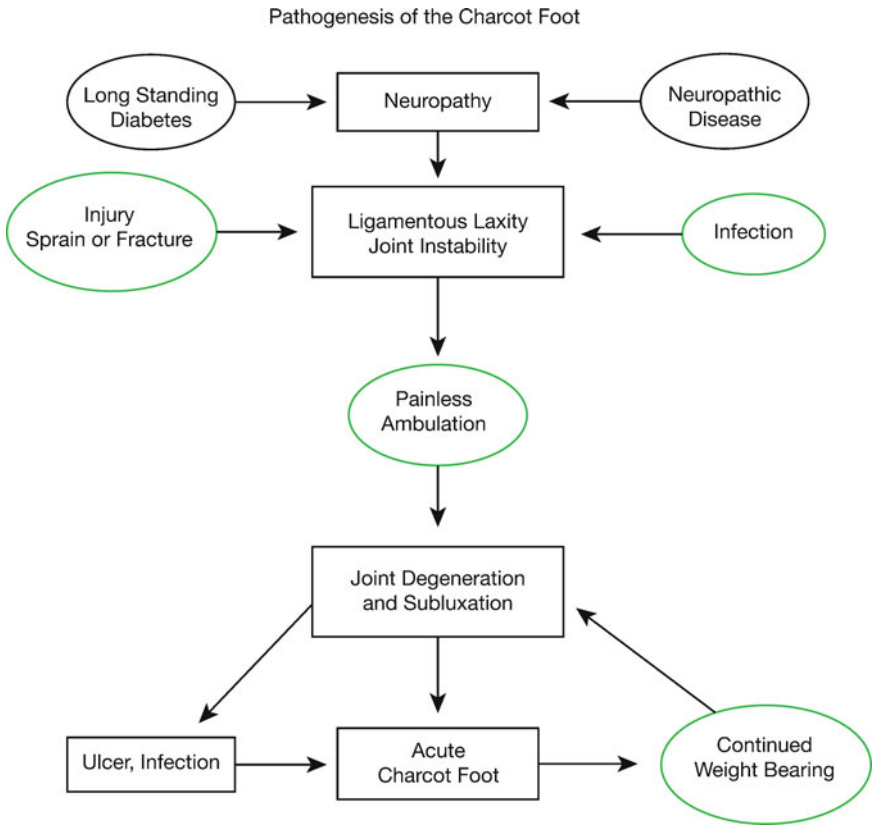

Fig. 20.1 Pathogenesis of diabetic neuropathic osteoarthropathy

neuropathic limb. The resultant osteolysis, demineralization, and weakening of bone can predispose to the development of neuroosteoarthropathy [2, 18, 20, 21, 24, 25]. Several studies have demonstrated reduced bone mineral density with an apparent imbalance between the normally linked bone resorption and production in patients with osteoarthropathy [26–28]. Specifically, greater osteoclastic than osteoblastic activity has been noted in acute neuroarthropathy, suggesting an explanation for the excessive bone resorption during the acute stage [21, 26].

The actual pathogenesis of Charcot arthropathy most likely is a combined effect of both the neurovascular and neurotraumatic theories [18, 24, 29]. It is generally accepted that trauma superimposed on a well perfused but severely neuropathic extremity can precipitate the development of an acute Charcot foot. Approximately 50% of those with Charcot foot recall some incipient trauma [30]. But the presence of sensory neuropathy can render the patient unaware of the initial precipitating trauma and often profound osseous destruction takes place during continued ambulation. The concomitant autonomic neuropathy with its associated osteopenia and relative weakness of the bone predisposes it to fracture [21, 27]. A vicious cycle then ensues where the insensate patient continues to walk on the injured foot, thereby allowing further damage to occur [9]. With added trauma and fractures in the face of an abundant hyperemic response to injury, marked swelling soon follows. Capsular and ligamentous distension or rupture is also a part of this process and leads to the typical joint subluxations and loss of normal pedal architecture culminating in the classic rocker-bottom Charcot foot. The amount of joint destruction and deformity which results is highly dependent upon the time at which the proper diagnosis is made and when non-weight-bearing immobilization is begun [9]. A simplified cycle of the pathogenesis of Charcot joints is illustrated in Fig. 20.1.

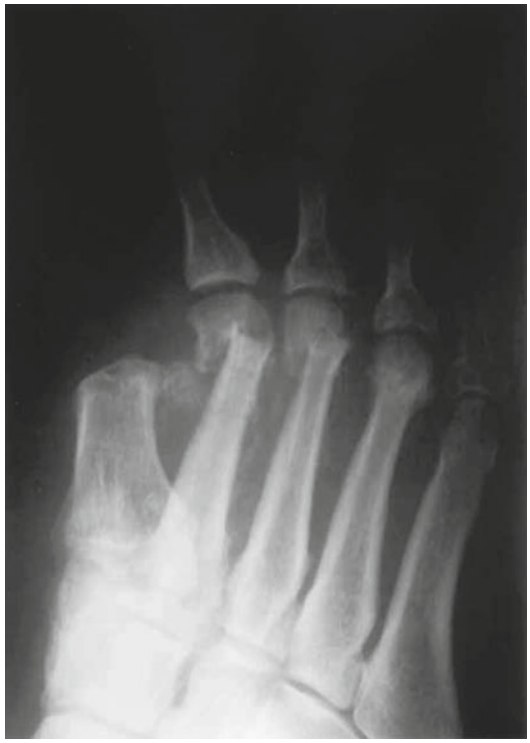

Fig. 20.2 Neuropathic changes (fractures) in the lesser metatarsal heads after undergoing a first ray amputation. Biomechanical imbalances and increased stress presumably lead to these changes

Often it is a fracture, either intra-articular or extra-articular, which initiates the destructive process. This had not been fully appreciated until Johnson presented a series of cases in which diabetic patients developed typical Charcot joints after sustaining neuropathic fractures [31]. Additionally, amputation of the great toe or first ray, often a consequence of infection or gangrene in the diabetic patient, may lead to neuropathic joint changes in the lesser metatarsophalangeal (MTP) joints (Fig. 20.2). Presumably, this is a stress related factor secondary to an acquired biomechanical imbalance. Intra-articular infection can also be implicated as an inciting event leading to this endpoint. In effect, almost any inflammatory or destructive process introduced to a neuropathic joint has the potential for creating a Charcot joint. Herbst et al. have recently reported their findings concerning the type of presentation as related to patients' bone mineral density (BMD) [31]. They found that patients with normal BMD had typical changes in the midfoot primarily comprised of joint dislocations. However, in those patients with reduced BMD, fracture patterns predominated in the ankle and forefoot.

Several authors have noted the similarities between the acute destructive phase in Charcot arthropathy and reflex sympathetic dystrophy (complex regional pain syndrome) [21, 22]. Both conditions are associated with an exaggerated vascular response as well as with the development of osteopenia. Both can also be related to previous acute trauma. While the underlying pathophysiological processes are not yet firmly established, both are marked by excessive osteoclastic activity and seem to respond well to treatment with bisphosphonates [21, 22, 32]. Jeffcoate has also suggested that a dysregulation of the RANK-L (receptor activator of nuclear factor kappa B ligand)/OPG (osteoprotegerin) signaling pathway and attendant affects on blood flow and bone turnover might also play a role in this regard [33, 34]. Further study is required, however, to determine how these pathways interact in patients with neuropathy to cause increased vascularity and subsequent osteopenia.

Classification of Charcot Arthropathy

The most common classification system of Charcot arthropathy is based on radiographic appearance as well as physiologic stages of the process. The *Eichenholtz classification* divides osteoarthropathy into developmental, coalescence, and reconstructive stages [35]. Several other authors have subsequently proposed an earlier *Stage 0* that corresponds to the initial inflammatory period following injury but prior to the development of characteristic bony radiographic changes [36–38]. This prodromal period might be considered as an "osteoarthropathy in situ" stage. The traditional *developmental* stage is characterized by fractures, debris formation and fragmentation of cartilage and subchondral bone. This is followed by capsular distension, ligamentous laxity, and varying degrees of subluxation and

marked soft tissue swelling. Synovial biopsy at this time will show osseous and cartilaginous debris embedded in a thickened synovium, which is pathognomonic for the disease [35]. The *coalescence* stage is marked by the absorption of much of the fine debris, a reduction in soft tissue swelling, bone callus proliferation and consolidation of fractures. Finally, the *reconstructive* stage is denoted by bony ankylosis and hypertrophic proliferation with some restoration of stability when this stage is reached. In certain cases, however, severe osseous disintegration occurs due to prolonged activity. In these situations the condition may be referred to as chronically active and little healing, if any, takes place. While the system is radiologically very descriptive and useful, its practical clinical applicability is less so. In clinical practice, the initial developmental stage is considered *active* or *acute*, while the coalescent and reconstructive stages are considered to be the *quiescent* or reparative stages. Other classification systems have been described based upon anatomic sites of involvement but do not describe the activity of the disease [37, 39–42]. Rogers and Bevilacqua described a prognostic classification based on anatomic location and complicating factors of the Charcot joint [42, 43]. Several other systems primarily focus on disorders of the midfoot and/or hind foot [39–41], while Sanders and Frykberg's classification includes involvement of the forefoot, midfoot, and rearfoot [2, 10].

Radiographic Findings

Radiographically, osteoarthropathy takes on the appearance of a severely destructive form of degenerative arthritis. Serial X-rays will customarily demonstrate multiple changes occurring throughout the process and can assist in monitoring disease activity. Rarely will nucleotide scanning, CT, or MRI be necessary to establish the diagnosis. The acute or developmental stage is marked by an abundance of soft tissue edema, osteopenia, multiple fractures, loose bodies, dislocations, or subluxations [29, 44]. These radiographic findings are fairly typical of noninfective bone changes associated with diabetes and have been described well by Newman [45]. In addition

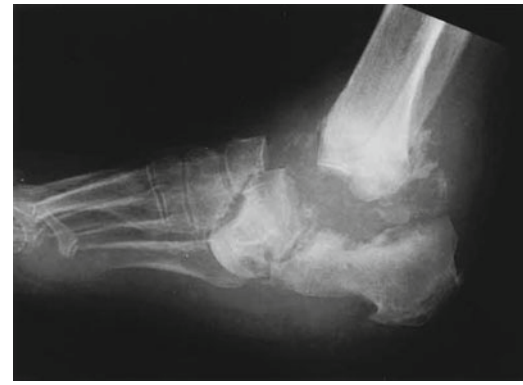

Fig. 20.3 Osteolysis of the talus and disintegration of the ankle and Subtalar joints

to alterations in the normal pedal architecture, the metatarsal heads and phalanges will frequently demonstrate atrophic changes often called diabetic *osteolysis*. Synonyms for this phenomenon include a "sucked candy" appearance, "pencil pointing," "hour glass" deformities of the phalanges, or mortar and pestle deformity of the MTP joints. Massive osteolysis can also occur in the rearfoot during the acute stage, especially in the ankle and subtalar joints (Fig. 20.3). These changes will often coexist with the obvious ankle fractures that initiated the destructive process. Medial arterial calcification is another associated, but unrelated, finding frequently observed in these patients [21].

Chronic reparative or quiescent radiographic changes include hypertrophic changes such as periosteal new bone formation, coalescence of fractures and bony fragments, sclerosis, remineralization, and a reduction in soft tissue edema [2, 31, 44, 45]. Rocker-bottom deformities, calcaneal equinus, dropped cuboid, or other deformities not previously appreciated may also become visible, especially when taking weight-bearing images. Table 20.2 summarizes the varieties of radiographic changes found in osteoarthropathy.

Sanders and Frykberg describe typical neuropathic osteoarthropathy patterns of joint involvement based upon joint location in diabetic patients [2]. These patterns may exist independently or in combination with each other as determined through clinical and radiographic findings. They are illustrated in Fig. 20.4 and described as follows: Pattern

Table 20.2 Radiographic changes in osteoarthropathy

Stage	Atrophic changes	Hypertrophic changes	Miscellaneous
Acute	Osteolysis—Resorption of bone Metatarsal heads, Phalangeal diaphyses, MTP, Subtalar, Ankle Osteopenia	Periosteal New Bone Intra-articular debris, Joint mice, fragments Osteophytes, Architectural collapse, Deformity	Joint Effusions Subluxations Fractures Soft tissue edema Medial arterial calcification Ulceration
Quiescent	Distal metatarsal and rearfoot osteolysis, Bone loss	Periosteal New Bone, Marginal osteophytes, Fracture bone callus Rocker bottom, Midfoot or Ankle deformity Ankylosis	Resorption of debris Diminished edema Sclerosis Ulceration

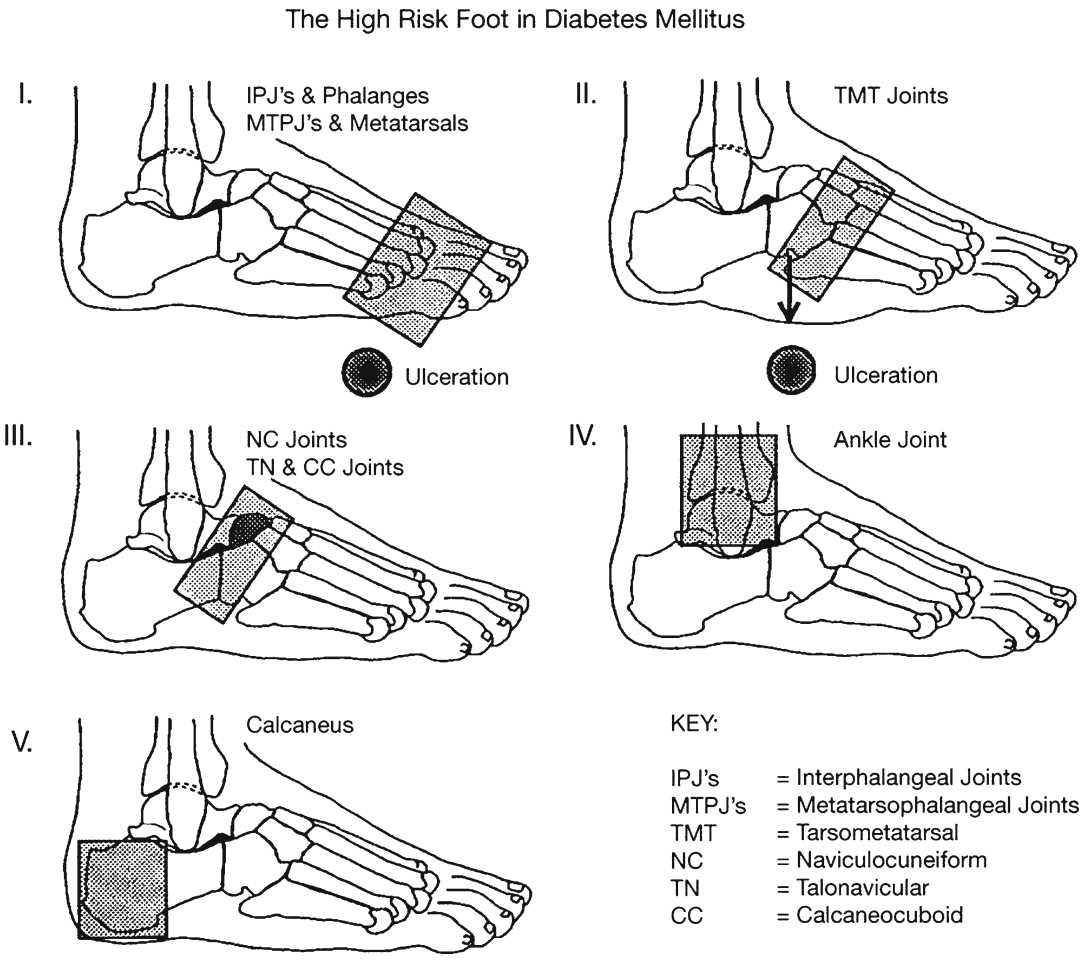

Fig. 20.4 Patterns of diabetic osteoarthropathy based on anatomic sites of involvement. (From Sanders LJ, Frykberg RG: Diabetic neuropathic osteoarthropathy: the Charcot foot, pp. 297–338 in Frykberg RG, editor: The High risk foot in diabetes mellitus, New York, 1991, Churchill Livingstone. Used with permission.)

I—Forefoot—Metatarsal-phalangeal joints, Pattern II—Tarsometatarsal (Lisfranc's) joint, Pattern III—Midtarsal and navicular-cuneiform joints, Pattern IV—Ankle and subtalar joints, and Pattern V—Calcaneus (Calcaneal Insufficiency Avulsion Fracture) [2, 29].

Pattern I: Forefoot

Pattern I encompasses atrophic changes or osteolysis of the metatarsophalangeal and interphalangeal joints with the characteristic sucked candy appearance of the distal metatarsals [25] (Fig. 20.5). Frequently, atrophic bone resorption of the distal metatarsals and phalanges accompanies other changes found in the midfoot and rearfoot. An infectious etiology has been proposed for these findings, although osteolysis can occur without any prior history of joint sepsis. Reports of 10–30% of the neuropathic osteoarthropathies have been categorized as Pattern I [2, 8].

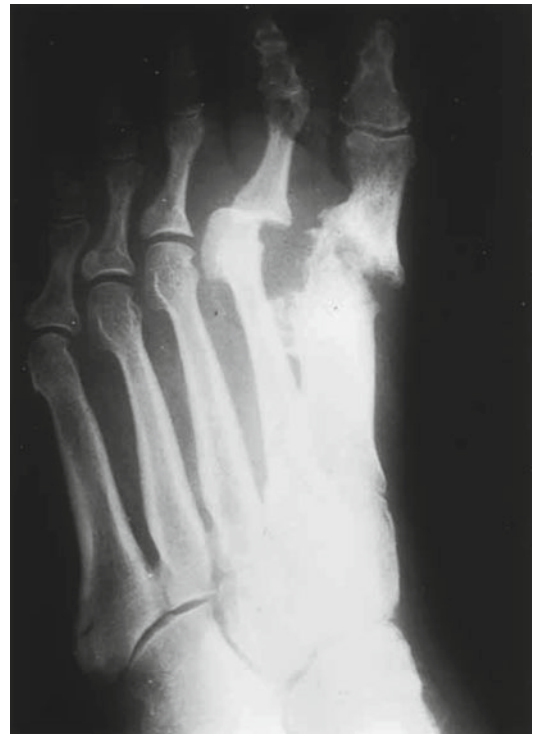

Fig. 20.5 Pattern I: osteolytic changes involving the first metatarsals and phalanx are evident without any current infection documented

Pattern II: Tarsometatarsal (Lisfranc's) Joint

Pattern II involves Lisfranc's joint, typically with the earliest clue being a very subtle lateral deviation of the base of the second metatarsal at the cuneiform joint. Once the stability of this "keystone" is lost, the Lisfranc joint complex will often subluxate dorsolaterally.

Fracture of the second metatarsal base allows for greater mobility in which subluxation of the metatarsal bases will occur. The rupture of intermetatarsal and tarsometatarsal ligaments plantarly will also allow a collapse of the arch during normal weight bearing, leading to the classic rocker-bottom deformity. Compensatory contracture of the gastrocnemius muscle will frequently follow and create a further plantarflexory moment to accentuate the inverted arch. This pattern also is commonly associated with plantar ulcerations at the apex of the collapse, which typically involves the cuboid or cuneiforms [2, 18, 25]. This was the most frequent pattern of presentation for diabetic Charcot feet in the Sinha series and represents the most common presentation in clinical practice (Fig. 20.6) [8].

Pattern III: Midtarsal and Naviculocuneiform Joints

Pattern III incorporates changes within the midtarsal (Chopart's) joint with the frequent addition of the naviculo-cuneiform joint. As described by Newman [45] and Lesko and Maurer [46], spontaneous dislocation of the talonavicular joint with or without fragmentation characterize this pattern. Newman further suggests that isolated talonavicular joint subluxation might even be considered as an entity separate from osteoarthropathy, although still an important element of noninfective neuropathic bone disease [45]. Lisfranc's joint changes (Pattern II) are often

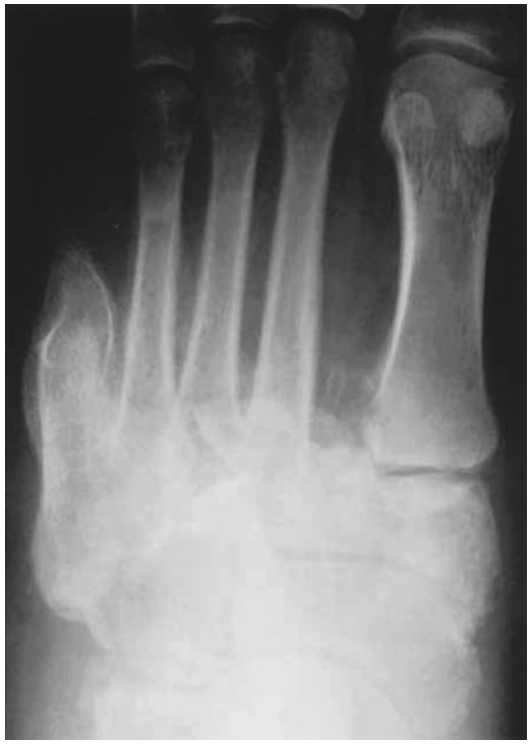

Fig. 20.6 Pattern II: Lisfranc's joint dislocation with associated fractures is evident in this common presentation of the Charcot foot. (Fifth ray had previously been amputated)

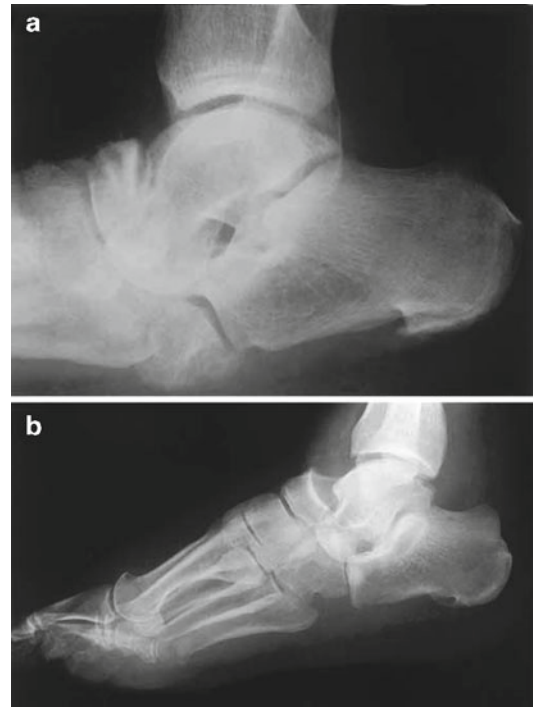

Fig. 20.7 Pattern III: (**a**) Talonavicular dislocation with "dropped cuboid" and plantarflexed calcaneus. (**b**) Talonavicular dislocation with early subtalar and calcaneal-cuboid subluxation. Note absence of fractures or osteochondral defects

seen in combination with Pattern III deformities of the lesser tarsus (Fig. 20.7).

Pattern IV: Ankle and Subtalar Joint

Pattern IV involves the ankle joint, including the subtalar joint and body of the talus (Fig. 20.8). Disintegration of the talar body is equivalent to the central tarsal disintegration of Harris and Brand [39]. The destructive forces are created by joint incongruity and continued mechanical stress which eventually erodes the talus. Massive osteolysis is frequently observed in this pattern with attendant ankle or subtalar subluxation and angular deformity. As noted, tibial or fibular malleolar fractures frequently are seen in association with osteoarthropathy in this location and most likely precipitated the development of the joint dissolution. Pattern IV Charcot is found in approximately 10% of reported cases [2, 8, 47].

Pattern V: Calcaneus (Calcaneal Insufficiency Avulsion Fracture)

Pattern V, the least common presentation (~2%), is characterized by extra-articular fractures of the calcaneus (posterior pillar). This osteopathy is usually included in the neuropathic osteoarthropathy classification, however, there is no joint involvement (Fig. 20.9). This is more appropriately considered as a neuropathic fracture of the body or, more commonly, the posterior tuberosity of the calcaneus. El-Khoury [48] and Kathol [49] have termed this entity the "calcaneal insufficiency avulsion fracture."

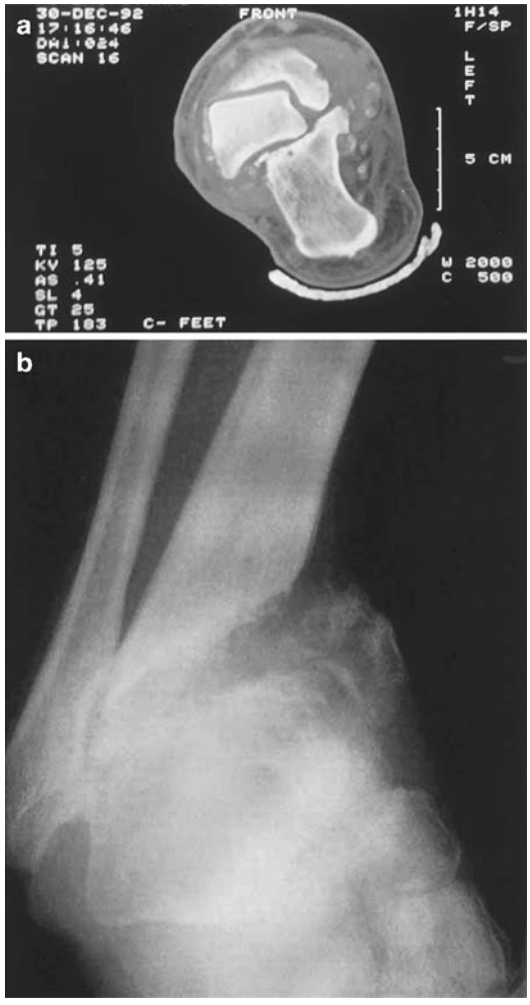

Fig. 20.8 Pattern IV: (**a**) Subtalar joint dislocation diagnosed on CT Scan. (**b**) Acute ankle Charcot with medial malleolar fracture and medial displacement of foot

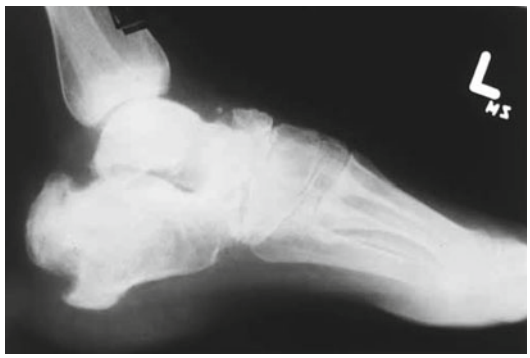

Fig. 20.9 Pattern V: Calcaneal insufficiency avulsion fracture of the calcaneus

Clinical Presentation

The classic presentation for acute osteoarthropathy includes several characteristic clinical findings (Table 20.3). Typically, the patient with a Charcot foot will have had a long duration of diabetes, usually in excess of 12 years. Although all age groups can be affected, a review of the literature in this regard indicates that the majority of patients are in their sixth decade (mid-fifties) [2, 18]. A recent report, however, indicates that there is an apparent age difference in onset between type 1 and type 2 diabetic patients [50]. Whereas the average age at presentation for the entire cohort and type 2 patients is indeed in the sixth decade, for type 1 patients the age at onset was in the fifth decade (forties). Patients with type 1 diabetes also demonstrated a longer duration of the disease than in type 2 diabetic patients with osteoarthropathy (24 years vs. 13 years) [50]. This has also been corroborated by an earlier report from Finland [51]. There does not appear to be a predilection for either sex. While unilateral involvement is the most frequent presentation, bilateral Charcot feet can be found in 9–18% of patients [4, 8].

The initial presentation for acute Charcot arthropathy is usually quite distinct in that a diabetic patient will seek attention for a profoundly swollen foot that is difficult to fit into a shoe (Fig. 20.10). Although classically described as painless, 75% of these patients will complain of pain or aching in an otherwise insensate foot [4]. Frequently, an antecedent history of some type of injury can be elicited from the patient [30]. When no such history is available, the precipitating event might simply have gone unrecognized in the neuropathic limb.

On examination, the pulses will be characteristically bounding even through the grossly edematous foot [18]. Occasionally, however, the swelling will obscure one or both pedal pulses. In concert with the hyperemic response to injury, the foot will also be somewhat erythematous and warm. The skin temperature elevation can be ascertained by dermal infrared thermometry and will contrast with the unaffected side by 3–8°C

Table 20.3 Clinical features of acute Charcot joint

Vascular	Neuropathic	Skeletal	Cutaneous
Bounding pedal pulse	Absent or diminished:	Rocker bottom deformity	Neuropathic ulcer
Erythema	Pain	Medial tarsal subluxation	Hyperkeratoses
Edema	Vibration	Digital subluxation	Infection
Warmth	Deep tendon reflexes	Rearfoot equinovarus	Gangrene
	Light touch	Hypermobility, crepitus	
	Anhidrosis		

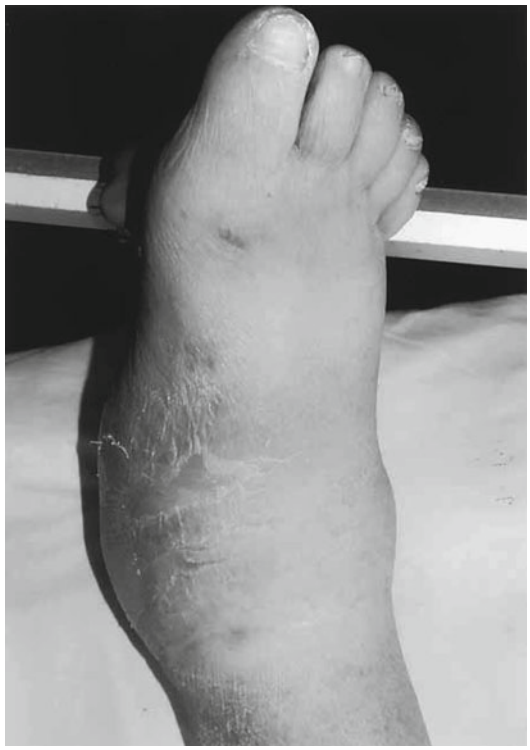

Fig. 20.10 Acute Charcot ankle with profound foot and leg edema

[2, 4, 47, 51, 52]. There is always some degree of sensory neuropathy in which reflexes, vibratory sense, proprioception, light touch, and/or pain (pin prick) are either diminished or absent. As mentioned, the patients will most often relate some localized pain although often mild in comparison to the deformity present. Motor neuropathy can present as a foot drop deformity or with intrinsic muscle atrophy. Triceps surae equinus can sometimes be ascertained initially, but cannot at this time be considered a precipitating or causal factor for osteoarthropathy. Autonomic neuropathy, which coexists with somatosensory neuropathy, can be clinically appreciated by the presence of anhidrosis with very dry skin and/or thick callus [21, 22]. Another fairly frequent cutaneous finding is a plantar neuropathic ulceration, especially in chronic or chronically active Charcot feet. A concomitant ulceration will therefore raise questions of potential contiguous osteomyelitis [18, 25, 29].

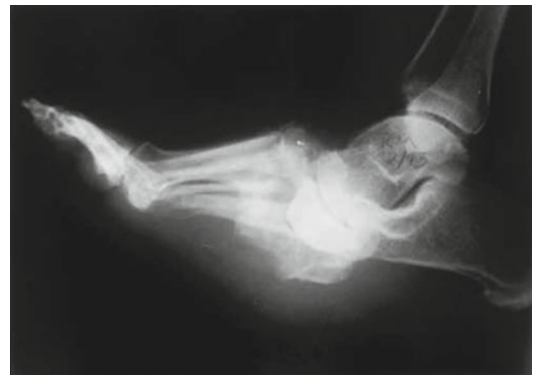

Fig. 20.11 Radiograph of rocker bottom Charcot foot with collapse of the midfoot

The skeletal changes frequently manifest as obvious deformity of the medial midfoot with collapse of the arch and/or rocker-bottom deformity (Fig. 20.11) [2, 29]. Associated findings might often include hypermobility with crepitus, significant instability, and ankle deformity.

Clinical Diagnosis of Acute Charcot Arthropathy

When presented with a warm, swollen, insensate foot, plain radiographs are invaluable in ascertaining the presence of osteoarthropathy [18, 53].

In most cases, no further imaging studies will be required to make the correct diagnosis. However, in the prodromal stage 0 there may be primarily soft tissue changes noted without evidence of distinct bone or joint pathology [54, 55]. Further investigation with scintigraphy, MRI, or serial radiographs should be considered when suspicion is high for osteoarthropathy [29, 54, 56–58]. With a concomitant wound, it may initially be difficult to differentiate between acute Charcot arthropathy and osteomyelitis solely based on plain radiographs [10, 59]. Additional laboratory studies may prove useful in determining the appropriate diagnosis. Leukocytosis can often suggest acute osteomyelitis; however, this normal response to infection can be blunted in persons with diabetes [60]. While the erythrocyte sedimentation rate (ESR) may also be elevated in the case of acute infection, it often responds similarly to any inflammatory process and is therefore nonspecific. When the ulcer probes to bone, a bone biopsy is indicated and should be considered as the most specific method of distinguishing between osteomyelitis and osteoarthropathy in these circumstances [18]. A biopsy consisting of multiple shards of bone and soft tissue embedded in the deep layers of synovium is pathognomonic for neuropathic osteoarthropathy [35].

Technetium bone scans are exquisitely sensitive for detecting Charcot arthropathy but nonetheless are generally nonspecific in assisting in the differentiation between osteomyelitis and acute Charcot arthropathy [54, 56, 61]. Indium scanning, while still expensive, has been shown to be more specific for infection [58, 61–63]. However, false-positive scans can frequently be found in a rapidly evolving acute osteoarthropathy without associated osteomyelitis. Additional studies helpful in differentiating Charcot arthropathy from osteomyelitis include Tc-HMPAO labeled white blood cell scans and magnetic resonance imaging [54, 57, 64, 65]. MRI examination can also be very sensitive to the earliest changes in neuroarthropathy, but again it is difficult to reliably detect bone infection superimposed upon the gross changes noted surrounding a Charcot joint [29, 54, 57, 66]. Another imaging modality that may show some promise in this regard is positron emission tomography (PET). Hopfner and colleagues have recently reported that this modality could not only detect early osteoarthropathy with 95% sensitivity but also reliably distinguish between Charcot lesions and osteomyelitis even in the presence of implanted hardware [66]. However, no study is 100% accurate in distinguishing neuropathic bone lesions from infectious entities. Inasmuch as clinical acumen is necessary for detecting Charcot arthropathy at its onset, clinical judgement remains of paramount importance in properly assessing and managing these patients.

Conservative Management

Immobilization and reduction of stress are considered the mainstays of treatment for acute Charcot arthropathy [4, 18, 29, 47, 53, 67, 68]. Non-weight-bearing on the affected limb for 8–12 weeks removes the continual trauma and should promote conversion of the active Charcot joint to the quiescent phase [18, 44, 51]. We advocate complete non-weight-bearing through the use of crutches, rolling knee walker, wheelchair or other assistive modalities during the initial acute period [68]. While it is an accepted form of treatment, three point crutch gait may in fact increase pressure to the contralateral limb, thereby predisposing it to repetitive stress and ulceration or neuroarthropathy [46]. A short leg plaster or fiberglass non-weight-bearing cast can additionally be used for acute Charcot events even in those patients with superficial uninfected ulcerations [4, 9]. A soft compressive dressing or Unna's Boot in concert with a removable cast walker or pneumatic walking brace can also be used effectively in this regard [29]. Following a relatively brief period of complete off-loading, a rapid reduction in edema and pain will occur. Although there is no uniform consensus, some centers advocate the initial use of a weight bearing total contact cast in the management of acute osteoarthropathy [4, 53, 69–72]. Such casts need to be changed at least weekly to adjust to the changes in limb volume as the edema decreases. When deeper or infected ulcerations are present,

frequent debridements and careful observation are required. These patients will therefore benefit from removable immobilization devices or bivalved casts.

Off-loading with or without immobilization should be anticipated for approximately 3–6 months, depending on the severity of joint destruction [4, 18, 47, 51]. Conversion to the reparative phase is indicated by a reduction in pedal temperature toward that of the unaffected side, and a sustained reduction in edema [2, 4, 18, 22, 47, 52]. This should be corroborated with serial radiographs indicating consolidation of osseous debris, union of fractures, and a reduction in soft tissue edema. McGill et al. have found a reduction in skin temperature and bone scan activity that mirrors activity of Charcot neuroarthropathy, both of which improve as the condition achieves quiescence [52].

When the patient enters the quiescent phase, management is directed at a gradual resumption of weight-bearing with prolonged or permanent bracing [4, 18, 44, 72]. Care must be taken to gradually wean the patient from non-weight-bearing to partial to full weight bearing with the use of assistive devices (i.e., crutches, cane, or walker). Progression to *protected* weight bearing is permitted, usually with the aid of some type of ambulatory immobilizing device [72]. Through the use of appropriately applied total contact casts or other immobilizing ambulatory modalities (i.e., fixed ankle walker, bivalved casts, total contact prosthetic walkers, patellar tendon-bearing braces, etc.), most patients may safely ambulate while bony consolidation of fractures progresses (Table 20.4) [18, 69, 73]. Charcot restraint orthotic walkers ("CROW") or other similar total contact prosthetic walkers have gained acceptance as useful protective modalities for the initial period of weight bearing [73, 74]. These custom-made braces usually incorporate some degree of patellar tendon bearing as well as a custom foot bed with a rocker sole. A more readily available option is a pneumatic walking brace or similar removable cast walker that might incorporate a cushioned foot bed or insole. These can be made nonremovable by simply applying adhesive tape or cast bandaging around the body of the walker to help encourage compliance (Fig. 20.12) [22, 74].

Table 20.4 Off-loading/immobilizing devices used in the management of Charcot feet

• Wheelchair
• Crutches
• Walker
• Elastic bandage or jones dressing
• Unna's boot
• Total contact cast
• Bivalved cast
• Posterior splint
• Fixed ankle walking brace
• Patellar tendon-bearing brace
• Charcot restraint orthotic walker (CROW)
• Surgical shoe with custom inlay

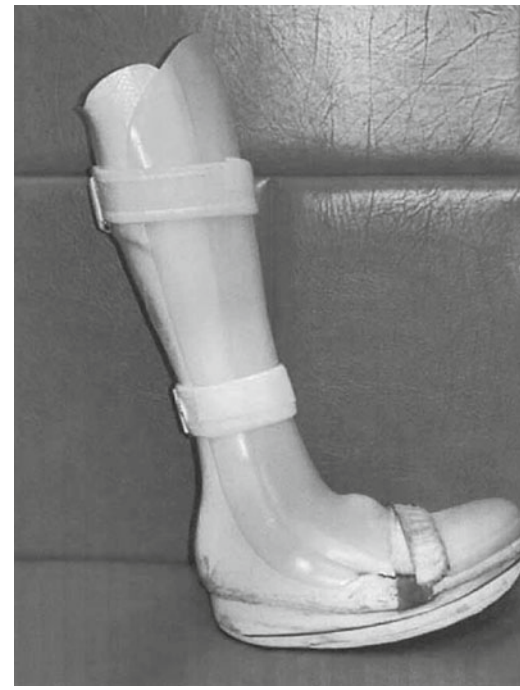

Fig. 20.12 Total contact custom orthosis with rocker sole

The mean time of rest and immobilization (casting followed by removable cast walker) prior to return to permanent footwear is approximately 4–6 months [2, 4, 47, 51, 53]. Feet must be closely monitored during the time of transition to permanent footwear to insure that the acute inflammatory

process does not recur. Forefoot and midfoot deformities (Patterns I–III) often do well with custom full-length inserts and comfort or extra depth shoes once bracing is no longer required [18]. Healing sandals made from full-length custom inserts placed into a surgical shoe often serve as interim footwear prior to wearing permanent footwear. Severe midfoot deformities will often require the fabrication of custom shoes to accommodate the misshapen foot. Rearfoot osteoarthropathy with minimal deformity may require only a deep, well cushioned shoe with a full-length orthotic device. For mildly unstable ankles without severe deformity or joint dissolution, high top custom shoes can sometimes provide adequate stability against transverse plane rotational forces. The moderately unstable ankle will benefit from an ankle foot orthosis (AFO) and a high top therapeutic shoe. The severely unstable or maligned rearfoot will require a patellar tendon bearing (PTB) brace incorporated into a custom shoe [69, 75]. The PTB brace has reportedly decreased the rearfoot mean peak forces by at least 32% [75].

In the setting of altered bone mineral density (BMD) in patients with diabetes and neuropathy, there has been recent interest in the adjunctive use of bisphosphonate therapy in acute Charcot arthropathy [21, 27, 32, 76, 77]. These pyrophosphate analogs are potent inhibitors of osteoclastic bone resorption and are widely used in the treatment of osteoporosis, Paget's disease, and reflex sympathetic dystrophy syndrome [21, 22]. Although one uncontrolled study of six patients found significant reductions in foot temperature and alkaline phosphatase levels as compared to baseline, its small size and lack of a control group preclude making any meaningful conclusions from the treatment [76]. A subsequent multicenter randomized trial in the UK from this same group was performed using a single intravenous infusion of pamidronate compared to saline infusion [32]. The treatment group had significant falls in temperature and markers of bone turnover (deoxypyridinoline cross links and bone-specific alkaline phosphatase) in subsequent weeks as contrasted to the control subjects. However, no differences in clinical or radiographic outcomes were reported. Trials of oral bisphosphonates with alendronate are have been done but effects of the treatment take 3–6 months which may not be sufficient in this limb-threatening disorder [22, 78]. Until definitive controlled outcome studies are performed which concurrently measure serum markers of osteoclastic activity and attempt to assess improvements in clinical and radiological healing, bisphosphonate therapy should be considered as simply an adjunctive therapy in acute osteoarthropathy that could *possibly* expedite conversion to the quiescent stage. Intranasal calcitonin is often used for osteoporosis has been shown to reduce markers of bone turnover and foot temperature differences in Charcot foot [79]. Some have theorized that it has a direct effect on RANK-L and may interrupt the deposition of calcium from the bone to the intima media of the blood vessels [33].

Another modality which has been applied to the management of acute neuroarthropathy is the use of bone stimulation [72, 80–82]. In one study of 31 subjects randomized to either casting alone or cast with Combined Magnetic Field (CMF) electrical bone stimulation, there was a significant reduction in time to consolidation of the Charcot joints in the study group (11 vs. 24 weeks) [81]. Low intensity pulsed ultrasound (LIPUS) has also been suggested as a useful adjunct in promoting healing of Charcot fractures, although this report only presented two cases of patients successfully treated after undergoing revisional surgery for recalcitrant deformities [83]. While both types of modalities have been proven successful in healing chronic nonunions or even fresh fractures (in the case of LIPUS), their efficacy in promoting prompt healing of acute Charcot fractures or union of surgical arthrodeses has yet to be proven by large, well controlled randomized clinical trials. Direct current implantable bone stimulators have shown benefit in Charcot foot reconstruction with arthrodesis [84].

Surgical Therapy

Neuropathic arthropathy should not be considered as primarily a surgical disorder. To the contrary, there is an abundance of support in the

literature confirming the need for initial attempts at conservative therapy to arrest the destructive process by converting the active Charcot joint to its quiescent, reparative stage [2, 4, 18, 47, 51, 69]. As indicated by Johnson in 1967, the three keys to treatment of this disorder should be prevention first, followed by early recognition, and once diagnosed, protection from further injury until all signs of "reaction" have subsided [31]. Surgery should be contemplated when attempts at conservative care as previously outlined have failed to provide a stable, plantigrade foot or in cases of gross dislocation. Additionally, when uncontrollable shearing forces result in recurrent plantar ulcerations or in those unusual cases that demonstrate continued destruction despite non-weight-bearing, procedures such as simple bone resections, osteotomies, midfoot or major tarsal reconstruction, and ankle arthrodeses might become necessary [31, 41, 53, 85–87]. However, a recent review of one center's experience with midfoot neuroarthropathy in 198 patients (201 ft) indicated that more than half of these patients could be successfully managed without the need for surgery [72].

Although becoming more common in clinical practice, surgery on the Charcot foot is not a new concept. Steindler, in 1931, first reviewed his series of operative results in tabetic patients including one subtalar arthrodesis [88]. He, like Samilson [89], Harris and Brand [39], and Johnson [90] many years later, recommended early recognition of the arthropathy, immediate protection from external deforming forces, and early operative stabilization when significant malalignment and instability precluded further conservative treatment. Samilson in 1959 [88] and Heiple in 1966 [91] were early to recognize the necessity for compressive internal fixation and prolonged immobilization in effectuating a solid bony fusion.

Harris and Brand in 1966 provided insight into this disorder associated with leprosy and described their five patterns of "disintegration of the tarsus" [39]. Full immobilization was always deemed imperative as an initial treatment, however, when progression continued or an unsatisfactory result was obtained, early surgical fusion was advocated. One year later Johnson published his large series which established the need for early recognition and protection to allow the acute inflammatory response to subside prior to surgical intervention [90]. As he stated, "Appropriate surgery on neuropathic joints, performed according to these principles, should be undertaken with great respect for the magnitude of the problem but not with dread." Johnson clearly favored osteotomy or arthrodesis in selected patients with quiescent Charcot joints and deformity in order to restore more normal alignment. Since the trauma of surgery could result in further absorption of bone during the acute stage, great emphasis was placed on resting the part until there was clinical and radiographic evidence of repair. Only then could surgery be attempted with a favorable chance for success [90].

Indications and Criteria

Instability, gross deformity, and progressive destruction despite immobilization are the primary indications for surgical intervention in neuroarthropathy [2, 18, 44, 92]. Additionally, recurrent ulceration overlying resultant bony prominences of the collapsed rear, mid, and forefoot may require partial ostectomy to effect final healing when performed in conjunction with appropriate footwear therapy [93, 94]. Pain or varying degrees of discomfort will frequently accompany the deformity and may be refractory to conservative care in some patients. Attributable to chronic instability, this can be effectively eliminated by limited arthrodeses at the primary focus of the neuroarthropathy (Fig. 20.13).

Lesko and Maurer [46] and Newman [45, 95] in their considerations of spontaneous peritalar dislocations advocate primary arthrodesis in those acute cases where there is a reducible luxation in the absence of significant osseous destruction. Since these luxations may be the initial event in the sequence leading to typical osteoarthropathy, early intervention following a period of non-weight-bearing has been recommended to counteract forces which would most likely lead to further progression of the deformity.

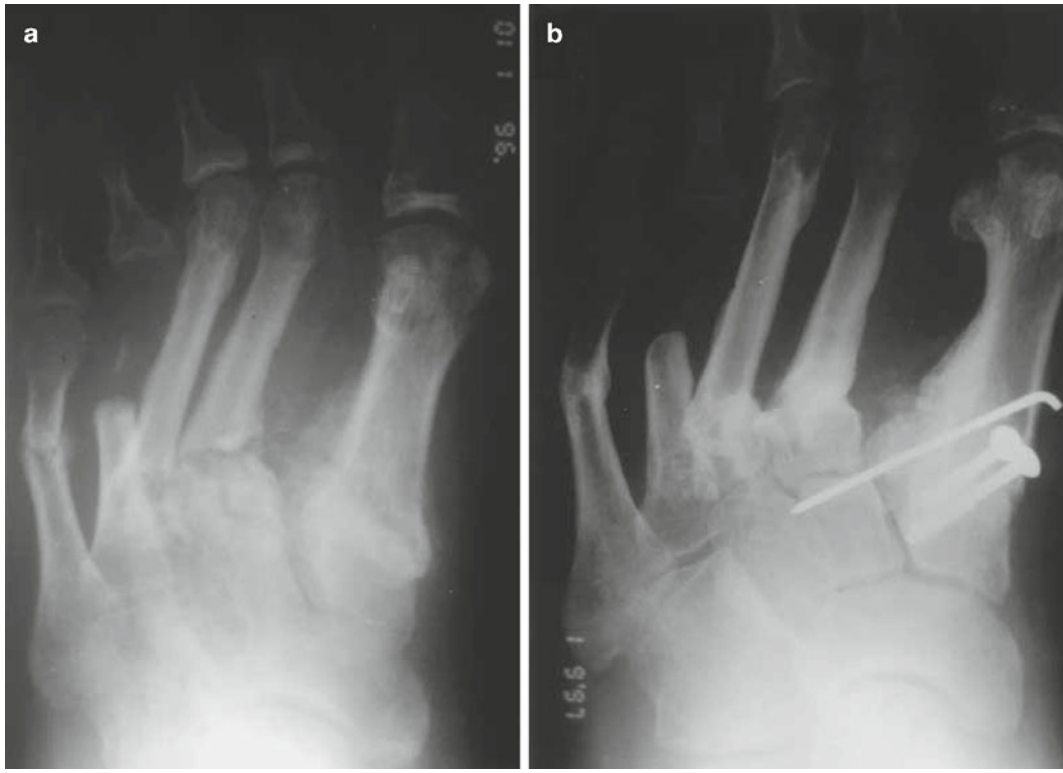

Fig. 20.13 (**a**) Preoperative X-ray of patient with dorsally dislocated 1st metatarsal-cuneiform joint and several metatarsal fractures. (**b**) Stability, resolution of symptoms, and complete healing was achieved with a limited arthrodesis of the first ray

Age and overall medical status should also weigh heavily in the decision regarding suitability for surgery. Recognizing that arthrodeses and major reconstructions will require cast immobilization and non-weight-bearing for 6 months or more, selection of the appropriate patient is critical to a successful outcome [4, 86, 87, 96]. Since the majority of patients with osteoarthropathy are in their sixth to seventh decades and may likely have coexistent cardiovascular or renal disease, careful consideration must be given to the risk versus benefit of lengthy operative procedures and the attendant prolonged recuperation [47]. As mentioned, a simple bone resection or limited arthrodesis might suffice in an older patient with a rocker-bottom deformity prone to ulceration as opposed to a complete reconstruction of the midfoot [25, 53, 94, 97]. The former procedures can be done under local anesthesia relatively quickly, require a shorter convalescence, are prone to fewer complications, and can provide a stable, ulcer free foot when maintained in protective footwear. Nevertheless, major foot reconstructions and arthrodeses are certainly indicated in those healthier patients with severe deformity, instability, or recurrent ulcerations who have not satisfactorily responded to conservative efforts [53, 96] (Fig. 20.14). In all cases, however, the patient must be well educated as to the necessity for strict compliance with post operative immobilization and non-weight-bearing for as long as 6–12 months.

An acute deformity, either a spontaneous dislocation or the more advanced fracture - dislocation paradigmatic of osteoarthropathy, must be rested and immobilized prior to any attempted surgery. Surgery during the active stage has the potential to compound and exacerbate the bone atrophy indicative of this inflammatory stage of destruction. Hence, it is often counterproductive as well as

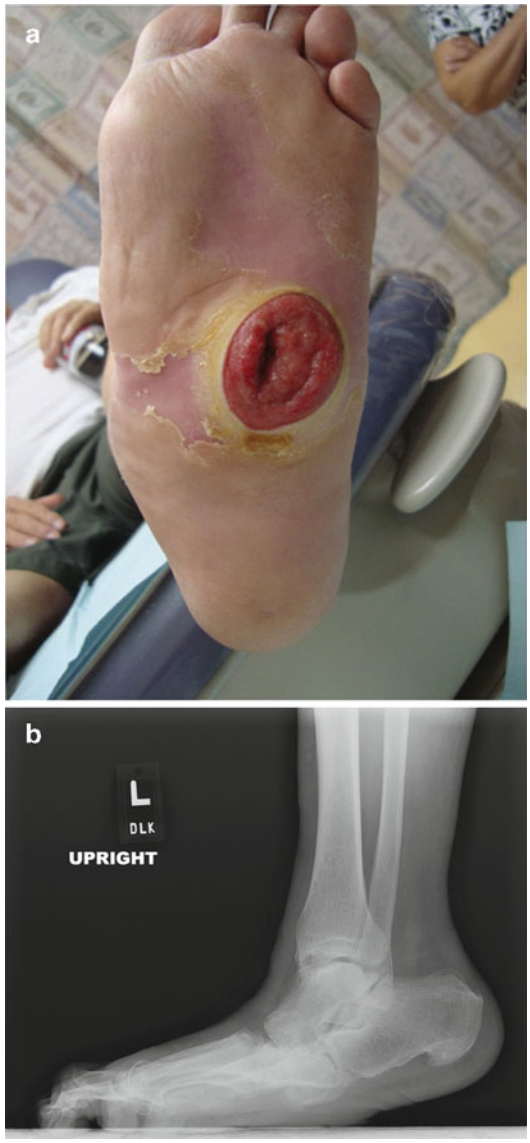

Fig. 20.14 (**a**) This patient has a chronic midfoot ulcer associated with a rocker-bottom deformity. (**b**) Radiograph of same patient showing severe rearfoot equinus and midfoot deformity

detrimental to operate on these feet until they have been converted to the quiescent, reparative stage. One small series, however, indicates successful arthrodesis rates with preserved foot function in patients with acute arthropathy of the midfoot [98]. Others have also advocated early operative repair with arthrodesis during stage 0 or stage 1, especially when nonoperative treatment has failed to prevent further deformity or arrest the destructive process [36, 99, 100]. Notwithstanding, this aggressive surgical approach needs confirmation through larger comparative trials prior to its adoption in the routine management of the acute Charcot foot. Overall, however, surgery performed primarily on chronic Charcot feet has met with increased success in recent years as experience develops. With an average union rate of 70% and improved alignment with stability, surgery on the neuroarthropathic foot has the potential not only to save limbs, but improve quality of life [53].

Ostectomy of plantar prominences in the face of recalcitrant or recurrent neuropathic ulceration is perhaps the most frequent procedure performed on Charcot feet [2, 94]. Such operations are fairly easy to perform and do not generally require lengthy periods of immobilization beyond attaining wound closure. Surgical approaches are varied, with direct excision of ulcers by ellipse or rotational local flaps predominating. Alternative incisions are performed adjacent to ulcers or prominences, either through a medial or lateral approach. One report suggests that excision of medial plantar prominences fare better and with fewer complications than those under the lateral midfoot [94]. However, an earlier study reviewing experience with only lateral column ulcers reported an 89% overall healing rate [97]. A flexible approach to both incision and soft tissue coverage, including tissue transfer, is therefore required for optimal outcomes in cases of midfoot plantar ulceration.

Arthrodesis of unstable Charcot joints of the midfoot and rearfoot frequently becomes necessary to provide a useful, plantigrade foot in those situations where bracing or footwear therapy have been unsuccessful [18, 31, 36, 101]. Major foot reconstruction is also an attractive alternative to amputation in patients with chronic or recurrent ulceration. Thompson et al. recommend reconstructive surgery for Charcot deformities unable to function with load sharing orthoses [102, 103]. Commonly, a tendo-Achilles lengthening precedes the fusion to ultimately diminish the plantarflexory forces contributing to pedal destruction [18, 53]. The traditional method for arthrodesis has been open reduction with solid

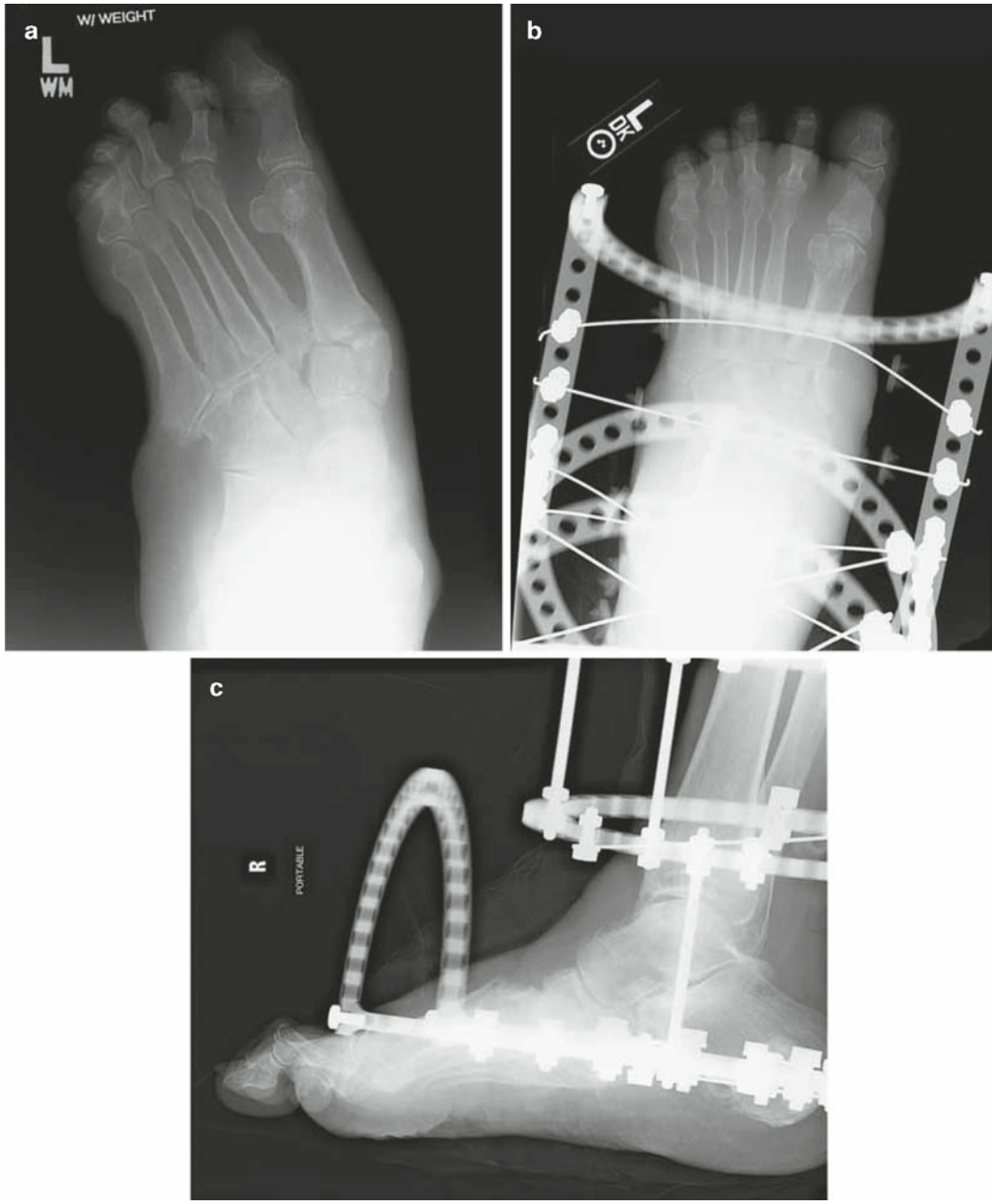

Fig. 20.15 Midfoot Charcot deformity corrected with circular external fixation. (**a**) Preoperative AP view showing midfoot deformity. (**b**) Postoperative AP view showing correction and frame in place. (**c**) Lateral postoperative X-ray with circular frame in place

internal fixation for noninfected Charcot joints, while external fixation is utilized when there is suspected infection of the joint fusion site [18, 31, 36, 103]. In recent years, however, there has been greater interest in using external fixation and circular (Ilizarov) frames for stabilization in the acute stage as well as chronic stage and maintenance of correction for major reconstructions (Fig. 20.15) [104–106]. Proposed benefits of circular frames include their ability to maintain

fixation even in osteopenic bone, early weight-bearing ability, avoidance of fixation devices at sites of ulceration and potential bone infection, the ability to correct severe deformities, and the capability for gradual adjustments in position and compression throughout the reparative process [104]. For ankle deformities requiring arthrodesis, some prefer to use retrograde intramedullary nails alone or in concert with external fixators to provide stability and enhanced rates of fusion [53, 107–109].

Operative fusion techniques vary by site, but generally require meticulous excision of the synovium, resection of sclerotic bone down to a healthy bleeding bed, open manipulation, and precise osteotomies prior to rigid fixation [31, 36, 39]. Tissue handling must be gentle to avoid undue trauma and dissection must be mindful of underlying neurovascular structures. After reduction of deformity temporary fixation is achieved with large Steinman pins, K-wires, or guidepins when cannulated screw systems are to be used [110]. After copious lavage, a surgical drain is placed before primary wound closure. External circular frames are generally constructed preoperatively and then applied with appropriate technique after wound closure.

Postoperative to internal fixation procedures, the patient immediately undergoes immobilization of the foot with a posterior splint or bivalve cast. The patient must adhere to strict bedrest and prevent lower extremity dependency for several days until the soft tissue swelling subsides and serial below knee casting begins. The patient will remain non-weight-bearing for a minimum of 2–3 months prior to considering partial weight bearing [4]. In general, protected weight bearing should be the rule for 6–12 months in order to avoid nonunion or late deformity in these difficult patients [36, 53]. After external fixation weight bearing status is variable—some surgeons allow limited or full weight bearing, while others choose to keep patients non-weight-bearing while the frame is in place. The contralateral extremity should be protected from the components of the external fixator which could cause injury. This can be accomplished by covering the external fixator or the contralateral extremity [111]. Advancement to weight-bearing cast, total contact cast, or walking brace will follow after evidence of consolidation. One reasonable approach is to remove the fixator after 2 months with subsequent application of an ambulatory total contact cast for several more months until there is evidence of radiographic consolidation [101]. Once healed, therapeutic footwear with or without bracing is necessary to prevent recurrent foot lesions.

Complications

Traditionally, surgery on neuropathic joints had been met with a good deal of failure including high rates of nonunion, pseudoarthrosis, and infection [2]. Most such occurrences can now be attributed to a failure of appreciation of the natural history of osteoarthropathy and lack of attention to the necessary criteria and the basic tenets of surgery on Charcot joints as previously discussed. Even with this knowledge, however, complications can ensue in these high-risk feet during the immediate postoperative period and beyond.

Infection can be a major sequel of surgery and of course can threaten the success of an attempted arthrodesis site as well as the limb itself. Most longitudinal studies and reports of surgery on Charcot joints indicate a certain percentage of patients in whom osteomyelitis or severe infection developed that necessitated major amputation [31, 47]. Therefore, caution must constantly be exercised in these patients to ensure that infection or osteomyelitis is controlled and eradicated prior to reconstructive surgery. Perioperative antibiotic therapy is certainly indicated in these compromised patients and once present, infection must be aggressively treated. With the use of external fixators comes the risk of pin tract infections or wire breakages requiring further surgery [112, 113]. Proper and timely management of complications does not change the outcome of the surgery.

Pseudoarthrosis and nonunion are very troublesome complications in nonneuropathic patients undergoing arthrodesis or osteotomy. However, this is not always the case in neuropathic patients

undergoing the same type of reconstructive procedures. As long as stability and satisfactory alignment are achieved, a failure of complete arthrodesis or union is not necessarily considered to be a failure of surgery [31, 53, 104]. Just as they will not sense the discomfort of posttraumatic arthritis in unreduced fracture-dislocations, these patients will have no symptoms from a stable, well-aligned nonunion. Nonetheless, the surgical principles for achieving solid union as previously discussed must always be followed when operating on these patients.

Since the trauma of surgery in itself can potentially incite an acute reaction in a chronic neuropathic joint, one must always treat the newly operated foot as an active Charcot joint. Furthermore, Clohisy makes a strong argument for prophylactic immobilization of the contralateral extremity to prevent the development of an acute deformity on the supporting foot [114]. Ablative or corrective procedures of the forefoot can also have detrimental effects on adjacent structures as well as on the midfoot and rearfoot [2]. Biomechanical alterations will result in increased areas of vertical and shear stress in new sites which will then be predisposed to ulceration and osteoarthropathy (Fig. 20.16). Therefore, surgery of any kind on the neuropathic foot must be performed with discretion and with attention to proper postoperative care to obviate the occurrence of these potentially destructive sequelae.

Amputation should usually be regarded as a procedure of last resort in neuropathic patients and not as a normal consequence of osteoarthropathy. While this outcome can sometimes represent a failure in early recognition and management, amputation usually results from overwhelming postoperative infection or late stage ulcerations. Unfortunately, amputation will always be a necessary consideration in this complicated group of patients [115]. In certain situations, amputation might be the *best* alternative to a difficult reconstruction in an unstable patient or in those patients who do not wish to engage in the lengthy recuperative period that follows major arthrodeses. However, this must be reserved for those extremities beyond salvage after all other attempts at conservative and reconstructive care have failed.

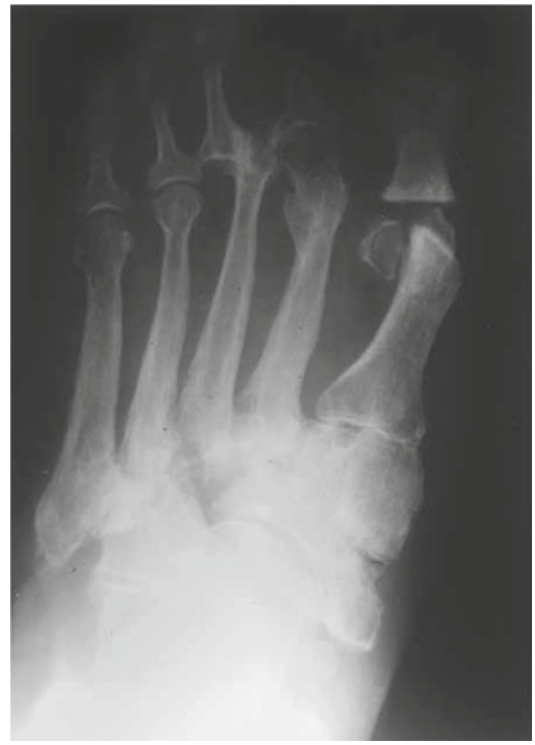

Fig. 20.16 Resection of the 1st MTP joint in this neuropathic patient eventually lead to the development of Pattern I, II, and III changes presumably due to biomechanical alterations

The Syme amputation can effectively be performed as a limb salvage measure in such patients when the heel pad is preserved (Fig. 20.17). This operation can result in a fully ambulatory patient with very rapid accommodation to the full-length prosthesis [115].

Conclusion

The Charcot foot is a very serious limb-threatening complication of diabetes that can be attributed to preexisting peripheral neuropathy compounded by trauma of some degree. Oftentimes, the diagnosis is missed which can lead to further destruction [116, 117]. With the attendant hypervascular response coupled with osteopenia, fractures and dislocations can rapidly evolve into severe foot deformities as a consequence of continued weight bearing. It is therefore incumbent upon the

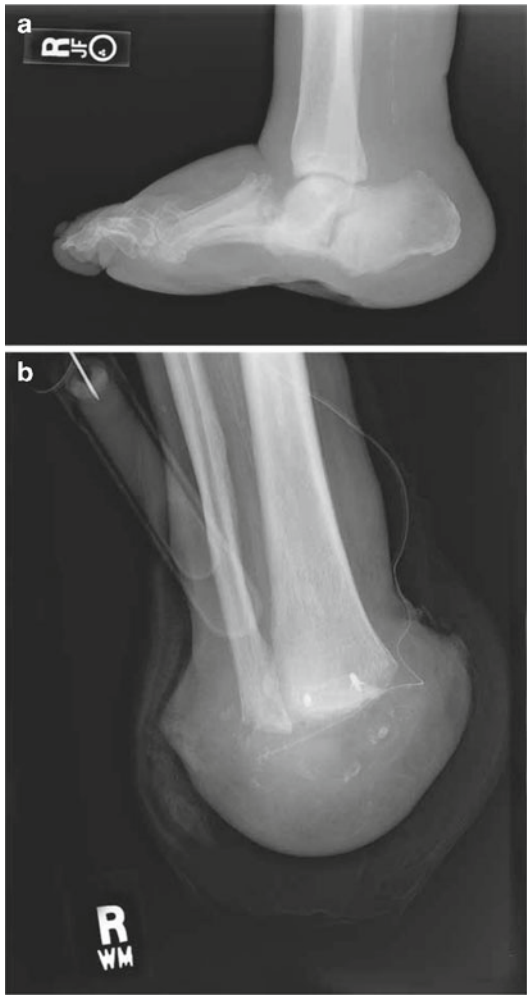

Fig. 20.17 (**a**) This patient had a chronic Charcot deformity with ulceration and recalcitrant osteomyelitis of the rearfoot for several years. (**b**) Postoperative X-ray of Syme amputation performed on same patient

practitioner to diagnose this process early in order to arrest the progression of the destructive phase and institute appropriate treatment. While non-weight-bearing and immobilization remain the mainstays of treatment in the acute stage, over the last decade there has been greater interest in surgical solutions for the severe deformities, recurrent ulcers, or instability that frequently results in later stages. As our knowledge and experience have grown, long-term outcomes have improved. As of yet, however, many questions remain unanswered pertaining to the precise mechanisms involved in the etiology of osteoarthropathy as well as those concerning optimal early and late stage treatments. With a heightened suspicion for the disorder, further prospective research, and an evidence-based approach to treatment, the future holds even greater promise for these patients.

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Soft Tissue Reconstructive Options for the Ulcerated or Gangrenous Diabetic Foot

21

Christopher E. Attinger and Mark W. Clemens II

Abstract

The complex biomechanics of the foot and ankle allow for a highly efficient and coordinated functional unit capable of nearly 10,000 steps a day. However, changes in sensation, motor function, skeletal stability, blood supply, and immune status render the foot and ankle susceptible to breakdown. Inability to salvage the injured foot traditionally has led to major amputation, carrying with it dramatic morbid sequelae and a lifetime dependence on prosthetic devices. Worldwide, a limb is lost to diabetes nearly every 30 s. Consequently, the relative 5-year mortality rate after limb amputation is greater than 50%, a startling figure when compared to mortality rates of lung cancer (86%), colon cancer (39%), and breast cancer (23%).

Because the foot and ankle is such a complex body part, salvage often demands a multidisciplinary team approach. This team ideally should consist of a vascular surgeon skilled in endovascular and distal bypass techniques, a foot and ankle surgeon skilled in internal and external (Ilizarov) bone stabilization techniques, a soft tissue surgeon familiar with modern wound healing as well as soft tissue reconstructive techniques, an infectious disease specialist to manage antibiotic therapy, and an endocrinologist to help manage the glucose levels. Surgical goals include transforming the chronic wound into an acute healing wound with healthy granulation tissue, neo-epithelialization, and wrinkled skin edges. This may include

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ensuring a good local blood supply, debriding the wound to a clean base, correcting any biomechanical abnormality, and nurturing the wound until it shows signs of healing. The subsequent reconstruction can then usually be accomplished by simple techniques, 90% of the time and complex flap reconstruction in 10% of cases. This chapter focuses on the critical aspects of limb salvage including evaluation, diagnosis, and treatment with a focus on flap-based reconstructions.

Keywords

Soft tissue reconstruction • Ulcerated foot • Ulcerated diabetic foot • Gangrenous foot • Negative pressure wound therapy • Debridement • Fasciocutaneous flaps • Temporary coverage • Cultured skin substitutes • Hyperbaric oxygen • Skin graft • Platelet-derived growth factor

Introduction

The complex biomechanics of the foot and ankle allow for a highly efficient and coordinated functional unit capable of nearly 10,000 steps a day. However, changes in sensation, motor function, skeletal stability, blood supply, and immune status render the foot and ankle susceptible to breakdown. Inability to salvage the injured foot traditionally has led to major amputation, carrying with it dramatic morbid sequelae and a lifetime dependence on prosthetic devices. Worldwide, a limb is lost to diabetes nearly every 30 s [1–3]. Consequently, the relative 5-year mortality rate after limb amputation is greater than 50%, a startling figure when compared to mortality rates of lung cancer (86%), colon cancer (39%), and breast cancer (23%) [4].

Because the foot and ankle is such a complex body part, salvage often demands a multidisciplinary team approach. This team ideally should consist of a vascular surgeon skilled in endovascular and distal bypass techniques, a foot and ankle surgeon skilled in internal and external (Ilizarov) bone stabilization techniques, a soft tissue surgeon familiar with modern wound healing as well as soft tissue reconstructive techniques, an infectious disease specialist to manage antibiotic therapy, and an endocrinologist to help manage the glucose levels. Surgical goals include transforming the chronic wound into an acute healing wound with healthy granulation tissue, neo-epithelialization, and wrinkled skin edges. This may include ensuring a good local blood supply, debriding the wound to a clean base, correcting any biomechanical abnormality, and nurturing the wound until it shows signs of healing. The subsequent reconstruction can then usually be accomplished by simple techniques, 90% of the time and complex flap reconstruction in 10% of cases. This chapter focuses on the critical aspects of limb salvage including evaluation, diagnosis, and treatment with a focus on flap-based reconstructions.

Establishing a Diagnosis

History

A thorough patient history is taken which should include the origin (usually traumatic) and age of the wound. The trauma is usually related to biomechanical abnormalities causing excessive local pressure during gait, changes in shoe wear, penetrating trauma or burn (hot sand or water bath). The patient's tetanus immunization status is obtained and the patient is inoculated if revaccination is indicated. It is important to ask what previous topical therapy was applied to the wound because certain topical agents can contribute to the wound's chronicity [5] (e.g., caustic agents such as hydrogen peroxide, 10% iodine, Dakin's solution, etc.). Finally, the nutritional status is assessed: their recent weight gain or loss, the

quality of their diet. Their smoking status is documented, and a complete list of medications and drug allergies are obtained.

A social history is then obtained to determine the level of activity, the level of home help available, and the type of work they are involved in. This can help to assess the patient's ability to comply with the treatment regimen because these wounds can involve up to 6 months of limited activity (i.e., Ilizarov treatment of a Charcot collapse). The diabetic patient's lack of compliance can be as high as 68% [6] is the single biggest reason for postoperative wound complications in excess of 20–55%.

Physical Examination

The wound is then assessed carefully by measuring its size and depth. The approximate area is obtained by multiplying the length of longest axis and by the width of the widest axis perpendicular to it. Depth is measured to assess the approximate volume. More accurate measurement is now possible through hand-held devices such as Aranz Silouhette laser camera (Christchurch, New Zealand) [7]. The exposed layers of tissue are documented: epidermis, dermis, subdermal fat, fascia, muscle tendon, joint capsule, joint, and/or bone. A metallic probe is used to assist in the evaluation of the depth of the wound. If the probe touches bone, there is an 85% chance that osteomyelitis [8] is present. If tendon is involved, the infection is very likely to have tracked proximally or distally. One should check for bogginess proximally and distally along the potentially involved tendon sheaths. If the suspicion is strong that a distal infection has spread proximally, the proximal areas where the tendon sheaths are readily accessible should be aspirated (i.e., extensor retinaculum, tarsal tunnel, etc.). The wound is then photographed.

If cellulitis is present, the border of the erythema is delineated with indelible ink. After debridement, deep cultures of the wound are obtained and broad spectrum antibiotics are started, the spread or retreat of the erythema can be continuously assessed. If, after 4–6 h, the cellulitis has extended beyond the inked boundary, either the antibiotics are inadequate and/or the wound has been inadequately debrided (Fig. 21.1). It is important not to confuse cellulitis with *dependent rubor* seen in patients with chronic ischemia or chronic wound. If the erythema disappears when the affected leg is elevated above the level of the heart, then the erythema is due to dependent rubor. With dependent rubor, inflammation is usually absent and the skin should have visible wrinkling. If the erythema persists despite elevation, the wound has surrounding cellulitis and needs antibiotic treatment ± debridement. Dependant rubor can also often seen at a fresh operative site and should not be confused with postoperative cellulitis. Again, rapid resolution of the erythema with elevation and presence of wrinkled skin at the incision edge indicate dependant rubor rather than cellulitis.

The blood flow to the area is then evaluated by palpation and/or hand-held Doppler [9]. The presence of palpable anterior and posterior tibial pulses suggests adequate blood flow. If one of the pulses is absent, then the pulses should be evaluated with a Doppler. If the quality of flow is questionable, a formal noninvasive arterial Doppler evaluation has to be performed. If the flow is inadequate, the patient should then be referred to a vascular surgeon who *specializes* in distal lower extremity endovascular and bypass revascularizations. In the face of undetermined or inadequate blood flow, debridement should be delayed until blood flow status has been assessed and corrected. However, immediate debridement is called for regardless of the vascular status when wet gangrene, ascending cellulitis from a necrotic wound, or necrotizing fasciitis is present. The wound can then be kept clean with dressing changes until revascularization. If the wound manifests progressive gangrene, maggots can be applied to locally debride necrotic tissue while the patient awaits revascularization [10, 11]. After successful bypass surgery, it then takes 4–10 days to maximize surrounding tissue oxygen level [12]. While it can take up to 3–4 weeks after endovascular revascularization.

Sensation must also be assessed. Lack of protective sensation can be established when the patient is unable to feel 10 g of pressure (5.07 Semms-Weinstein monofilament). This is critical

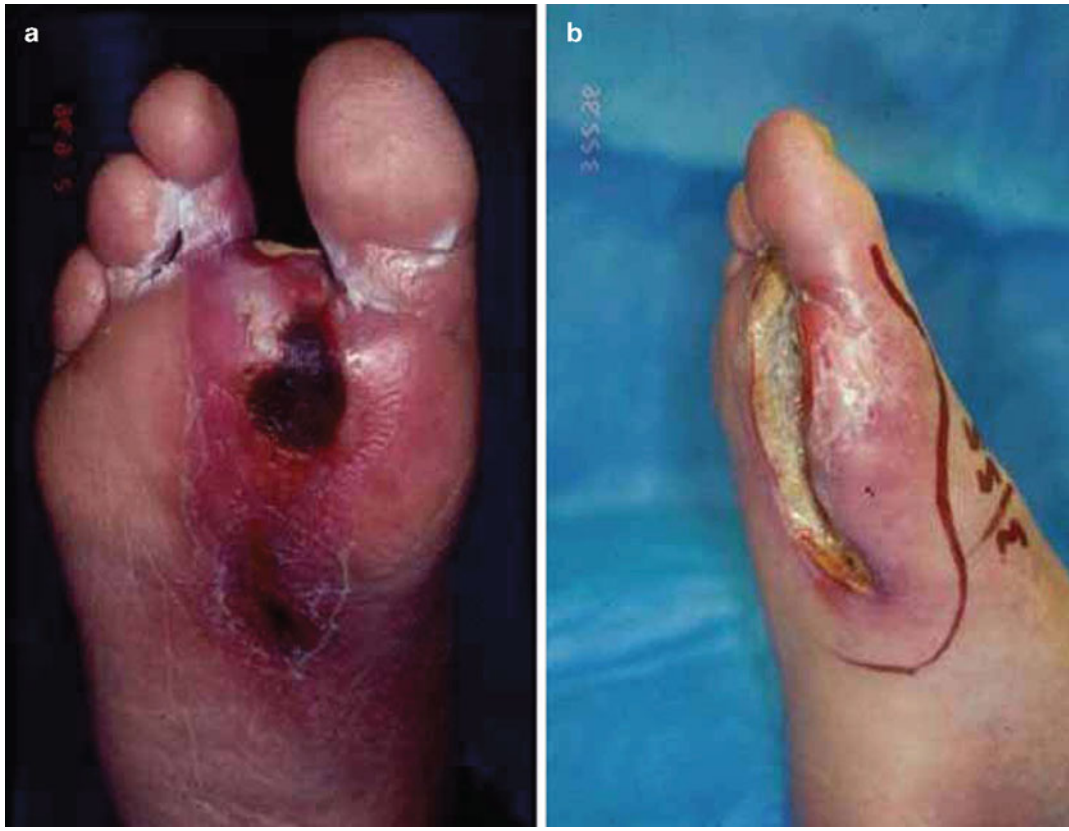

Fig. 21.1 If a foot presents with cellulitis (**a**), the border of the erythema is delineated and dated with indelible ink. If there is necrosis or ulceration, the wound should be debrided. After debridement, deep cultures of the wound are obtained and broad spectrum antibiotics are started. The delineated borders of the initial erythema are then assessed. If, after 4–6 h, the cellulitis has extended beyond the inked boundary, either the antibiotics are inadequate and/or the wound has been inadequately debrided. In this case, the redness has receded and therefore the initial therapy is appropriate (**b**)

to help understand the etiology of the ulcer, determine offloading regimens, and prevent ulceration with more vigilant follow-up [13].

The biomechanical abnormality caused by motor dysfunction, skeletal abnormalities, and/or a tight Achilles tendon causes high focal plantar pressures during gait. The local tissue at those sites in the insensate patient eventually breaks down under the repetitive stress of normal ambulation (on average, a person takes 10,000 steps a day). The motor neuropathy is most often seen in the intrinsic muscles of the foot with resultant hammer toe formation. Skeletal abnormalities can include a prominent metatarsal head, Charcot collapse, etc. These are best evaluated by weight-bearing X-ray views.

Because the elasticity of the Achilles tendon is affected by diabetes as elevated glucose levels bind to the collagen, it should also be carefully evaluated [14]. The patient's ability to dorsi-flex the supinated foot tests the elasticity of the Achilles tendon (Fig. 21.2). If the patient can dorsi-flex the foot more than 15° with the leg straight and bent, then the tendon has sufficient plasticity. If the foot can only be dorsi-flexed when the leg is bent, then the Gastrocnemius portion of the Achilles tendon is tight. If the foot cannot dorsi-flex when the leg is straight or bent, then both the Gastrocnemius and Soleus portions of the Achilles tendon are tight. Open or percutaneous release of the Achilles tendon [15] decreases forefoot pressure in the equino-varus

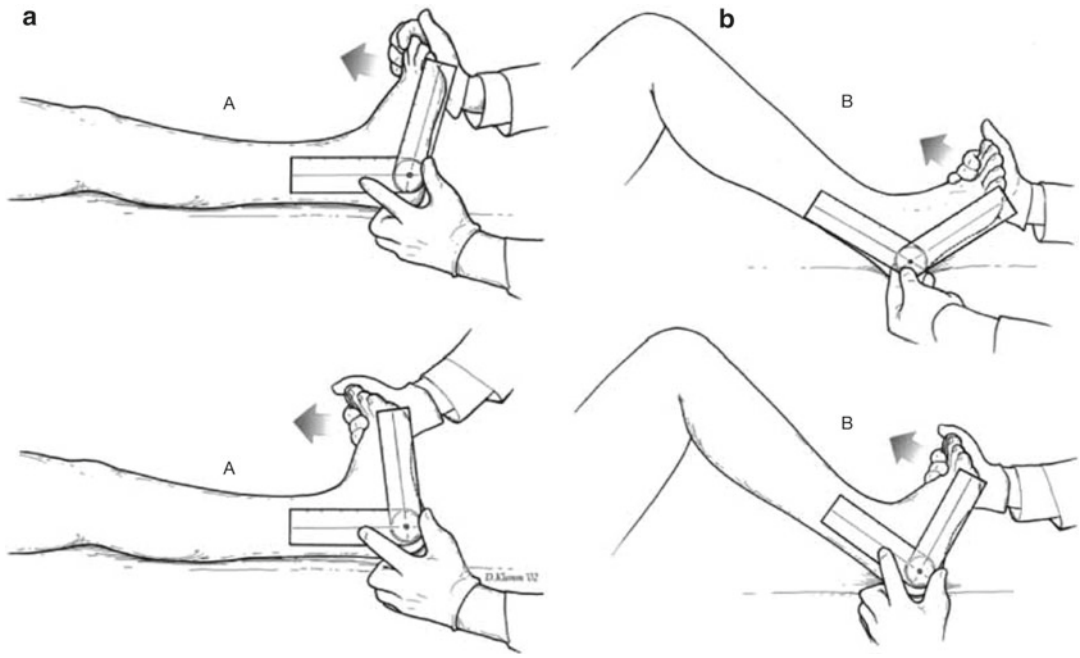

Fig. 21.2 The patient's ability to dorsi-flex the supinated foot tests the elasticity of the Achilles tendon. If the patient can dorsi-flex the foot more than 15 degrees with the leg straight (**a**) and bent (**b**), then the tendon has sufficient plasticity. If the foot can only be dorsi-flexed when the leg is bent, then the Gastrocnemius portion of the Achilles tendon is tight

foot during gait sufficiently to allow for the rapid healing of plantar forefoot ulcers. The release results in a permanent decrease in push-off forces which has been shown to decreasing ulcer recurrence rate from 86% to under 50% at 25 months out from surgery [16, 17]. Unless correction of the underlying biomechanical abnormality is part of the entire treatment plan, debriding and good wound care may prove futile.

Testing

Blood work should be obtained. The immediate blood glucose level and chronic glucose level (hemoglobin A1C) should be assessed. Hemoglobin A1C over 6% indicate poor control of blood glucose levels (7% = avg. plasma glucose level of 170 mg/dl, 8% = 205, 9% = 240, 10% = 275, and 11% = 310). High blood sugar in the face of a low hemoglobin A1C can indicate acute infection. The white blood cell count and differentiation is also very helpful in monitoring systemic infection. The numbers, however, can look deceptively normal in renal failure diabetic patients. A sedimentation rate can be helpful as a tracking tool during treatment of an infection. The kidney function should be evaluated especially since many of these patients may require an angiogram.

An X-ray is critical to evaluate the underlying bone architecture. It may not pick up acute osteomyelitis because it can take up to 3 weeks for osteomyelitis to appear on X-ray. An MRI or nuclear scan is usually superfluous if the surgeon plans to evaluate the affected bone during the debridement. However, these studies can be useful when the extent of osteomyelitis in the suspected bone is unclear or when there is suspicion that other bones may be involved.

Noninvasive arterial studies are useful adjuncts to help assess the quality of blood flow to the foot. Ankle–brachial indices are inaccurate in diabetics because their arterial walls calcify which then prevents the cuff from compressing the vessel. Because of the calcification, an ABI of

<0.9 is deemed abnormal [18]. Because the digital arteries are less likely to calcify, toe pressures higher than 50 mmHg indicate adequate flow. Pulse volume recordings that contain at least 15 small boxes in height indicate adequate arterial flow volumes. Tissue oxygen levels can be very useful if the laboratory tests them reliably. Levels lower than 20 mmHg indicate poor healing potential, level between 20 and 40 mmHg indicate possible healing and levels higher than 40 mmHg indicate good healing potential. Skin perfusion pressures have also been used successfully to predict the healing potential of a wound or amputation level [19]. Since no one test is totally accurate, the combination of all the above tests help provide the clinician with a more complete picture of the actual blood flow.

Debridement

The Role of Debridement in Wound Healing

Debriding a wound is defined as removing necrotic tissue, foreign material, and infecting bacteria from wound. Necrotic tissue, foreign material, and bacteria impede the body's attempt to heal by producing or stimulating the production of proteases, collagenases, and elastases that overwhelm the local wound healing process [20]. In this process, the building blocks (chemotactants, growth factors, growth receptors, mitogens, etc.) necessary for normal wound healing are destroyed. This hostile environment is one in which bacteria can proliferate and further inhibit wound healing. Bacteria produce their own wound inhibiting enzymes as well and consume many of the scarce local resources (oxygen, nutrition, and building blocks) that are necessary for wound healing. Most of the bacteria in chronic wounds reside within a glycocalyx (biofilm) that protects them from destruction by antibiotics and/or WBC [21]. The importance of debridement was re-emphasized when Steed reviewed the data of platelet-derived growth factor's effect on the healing of chronic diabetic wounds [22] and observed that wounds healed far more successfully when the wound debridement was performed weekly rather than more sporadically.

When debriding, use atraumatic surgical techniques to avoid damaging the healthy tissue left behind. Such tissue should be protected as it is the source of growth factors, nutrients, and building blocks required for subsequent healing. To leave a maximal amount of viable tissue behind, avoid traumatizing techniques such as crushing the skin edges with forceps or clamps, burning tissue with electrocautery, or tying off large clumps of tissue with sutures [23]. Chronic wounds have senescent cells at the edge of the wound that prevent healing [24]. Removal of 3–4 mm of the wound edge in these cases is as important as debriding the wound base to get the wound to heal.

The principal debriding technique consists of removing the grossly contaminated or ischemic tissue en masse. Surgical tools include a scalpel blade, mayo scissors, curettes, and rongeurs as well as power tools including a sagittal saw and a power burr. However, when approaching viable tissue, the technique is to take thin slices of tissue after thin slices of tissue until only normal tissue remains (Fig. 21.3). It is very helpful to use tissue color as a guide; at the end of a successful debridement, only three colors should remain in the wound base: red, yellow, and white. Curettes with sharp edges are very helpful for removing the proteinaceous coagulum that accumulates on top of both fresh and chronic granulation tissue (Fig. 21.4). A curette will not remove the biofilm that spreads deep to the wound along the blood vessel providing nutrition to the wound base in a process called perivascular cuffing. Deeper debridement or mechanical energy such as ultrasound is necessary to address that.

Also valuable to debridement is the hydro-surgical debrider (Versa-Jet,© Smith & Nephew, Hull, UK) that uses a high power water jet (up to 15,000 psi) to debride tissue (Fig. 21.5). The Venturi effect caused by this high pressure water jet stream sucks the underlying tissue into the stream of water and separates it from the underlying tissue. The hydro-surgical debrider works rapidly to take thin slice after thin slice of tissue with minimal surrounding tissue trauma.

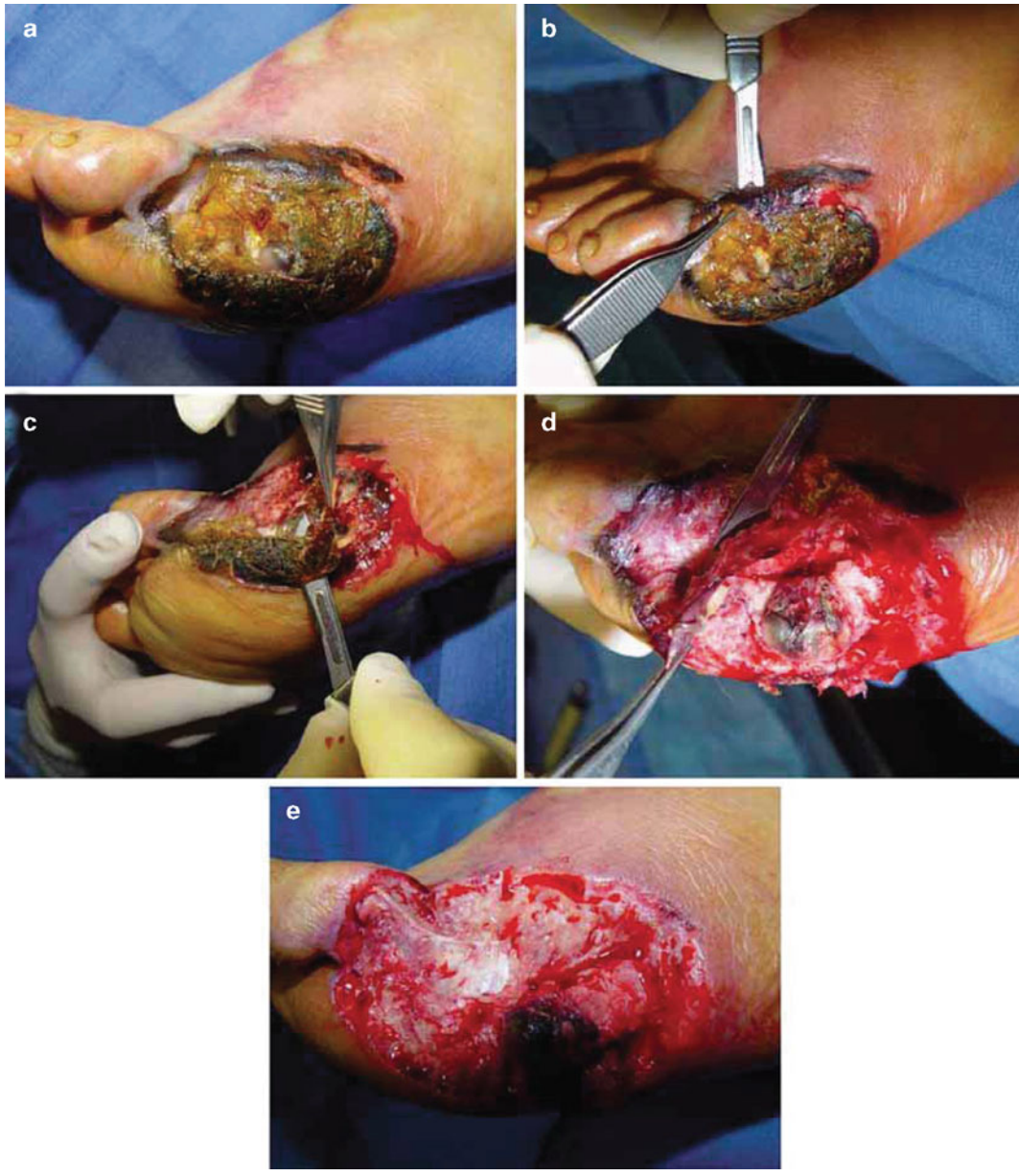

Fig. 21.3 The debridement technique that minimizes the risk of taking normal tissue is to take thin slices after thin slices of necrotic tissue until only normal tissue remains. Using the normal color of tissue as a guide, one should stop the debridement when the underlying tissue only contains healthy red, white, or yellow colored tissue. Grasp the tissue to be removed with the pickup and use a #10 or a #20 blade to slice off thin layer after thin layer. Change surgical blades frequently, as they dull quickly. Note that the *last picture shows* normal colored tissue except for the black distal metatarsal that still needs to be sawed off

It is helpful to paint the wound surface with methylene blue dye before applying the Versa-Jet. The disappearance of all the blue dye ensures that the wound surface has been entirely debrided as it can be easy to miss small areas. These small areas are likely to contain the residual biofilm or bacteria that then repopulate the wound. The chief advantage of the Versa-Jet is that it allows

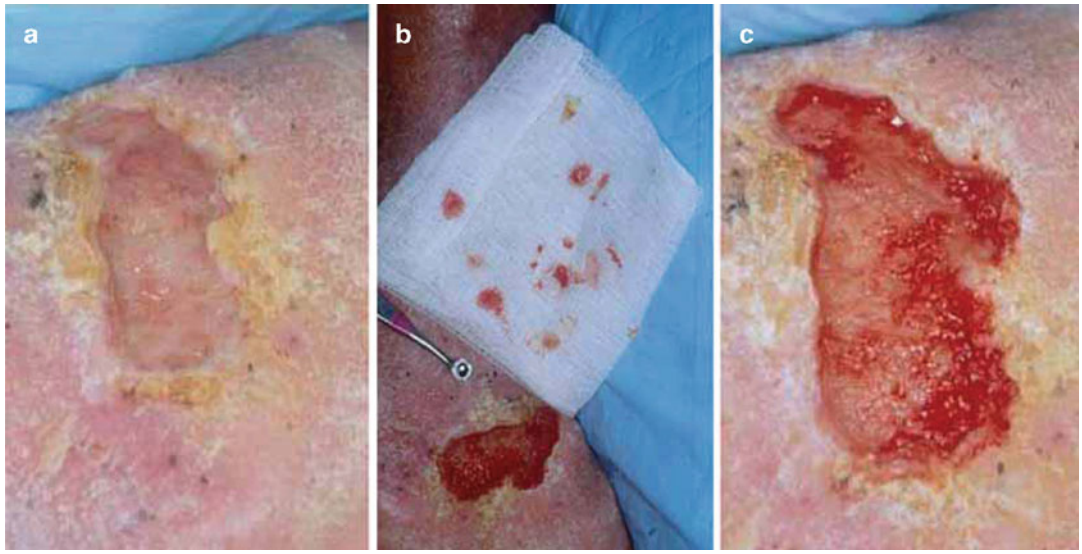

Fig. 21.4 Curettes with sharp edges are very helpful for removing the proteinaceous coagulum and superficial biofilm (**a**) that accumulates on top of chronic granulation tissue. A curette is a useful tool to remove that coagulum/biofilm (**b**). Since the coagulum contains a high concentration of metallo-proteases and biofilm, its removal diminishes the factors that have allowed the inflammatory phase to persist. (**c**) It is important to note that a curette does not remove the biofilm that is present below the surface of the wound which requires other methods to address it

for a very accurate control of the depth of cut and hence minimizes the risk of accidentally removing viable tissue. It is also very useful in preparing smooth recipient wound beds for skin grafts.

Debridement should be performed as often as necessary until the wound is deemed clean and ready for reconstruction. The wound is watched closely and re-debrided as long as there is devitalized tissue. The use of bio-surgery with maggots is an extremely effective alternative to debriding a wound when the patient cannot tolerate surgery, debriding dressings (wet to dry), or biosurgical agents (Fig. 21.6) [4, 5]. Maggots are the larvae of the *Phaenicia sericata* (green blow fly) and are irradiated so that they cannot metamorphose into the pupae phase. Thirty maggots consume 1 g tissue/day, consuming only necrotic tissue and bacteria and leaving any viable tissue intact. Maggots are painless and are very effective against antibiotic-resistant organisms. Maggots are the only agents that destroy all antibiotic-resistant bacteria including *MRSA* or *VRE*. They are applied on the wound and covered with a semipermeable dressing. They are changed every 2 days. However, to use them, one must first obtain the cooperation of both the patient and hospital staff.

In-between debridements, topical antibiotics can help reduce the bacterial load: silver sheeting (Acticoat,© Smith & Nephew, Hull, UK) or silver-sulfadiazine works well for all wounds. For draining wounds, iodosorb or silver containing hydrocolloids work well. Bactroban© is useful for MRSA, ¼ strength Acetic acid or gentamycin ointment for Pseudomonas infections, bacitracin for minimally infected wounds. To address biofilm, a variation of iodosorb, silver, lactoferrin all work well. Alternatively, the vacuum-assisted closure device (VAC©) can be applied *post debridement* to help control the bacterial flora assuming that the wound base is clean [25].

What to Debride

Remove nonviable skin as soon as possible unless revascularization is pending. If the border between live and dead tissue is clearly demarcated, excise the skin just beyond that border. Clotted venules at the skin edge indicate that the

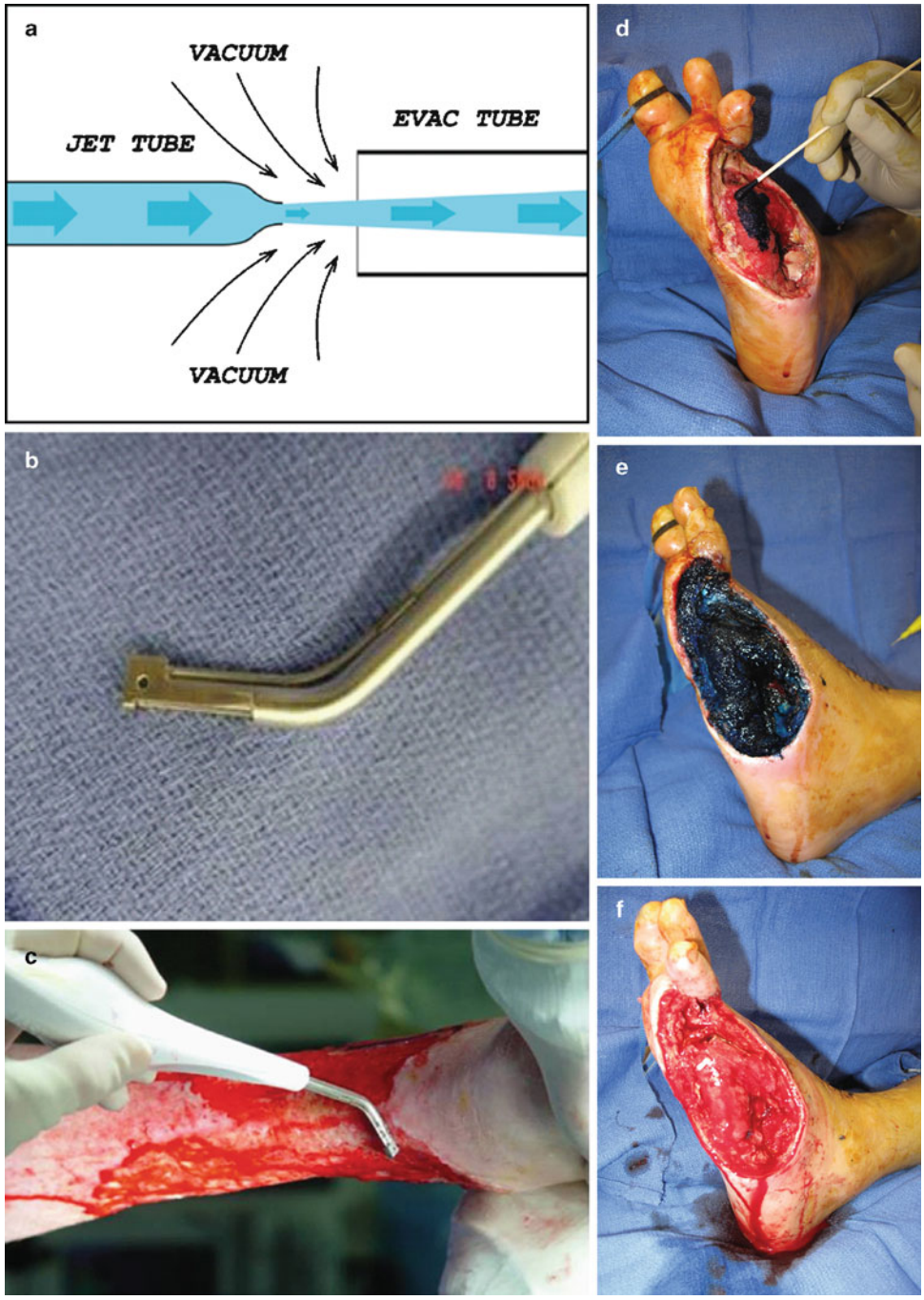

Fig. 21.5 The hydro-surgical debrider (Versa-Jet©, Smith & Nephew, Hull, UK) uses a high power water jet (up to 15,000 psi) to debride tissue. The Venturi effect caused by this high pressure water jet stream sucks the underlying tissue into the stream of water and separates it from the underlying tissue (**a**). The debrider (**b**) should be moved back and forth rapidly as it takes thin slice after thin slice of tissue with minimal surrounding tissue trauma (**c**). In order to ensure that the entire wound surface has been addressed, it is useful to paint the surface of the wound with methylene blue (**d**, **e**) and debride until all the blue is gone (**f**). Of course, the base of the wound should only have normal colors at its base including *yellow*, *red*, and *white*

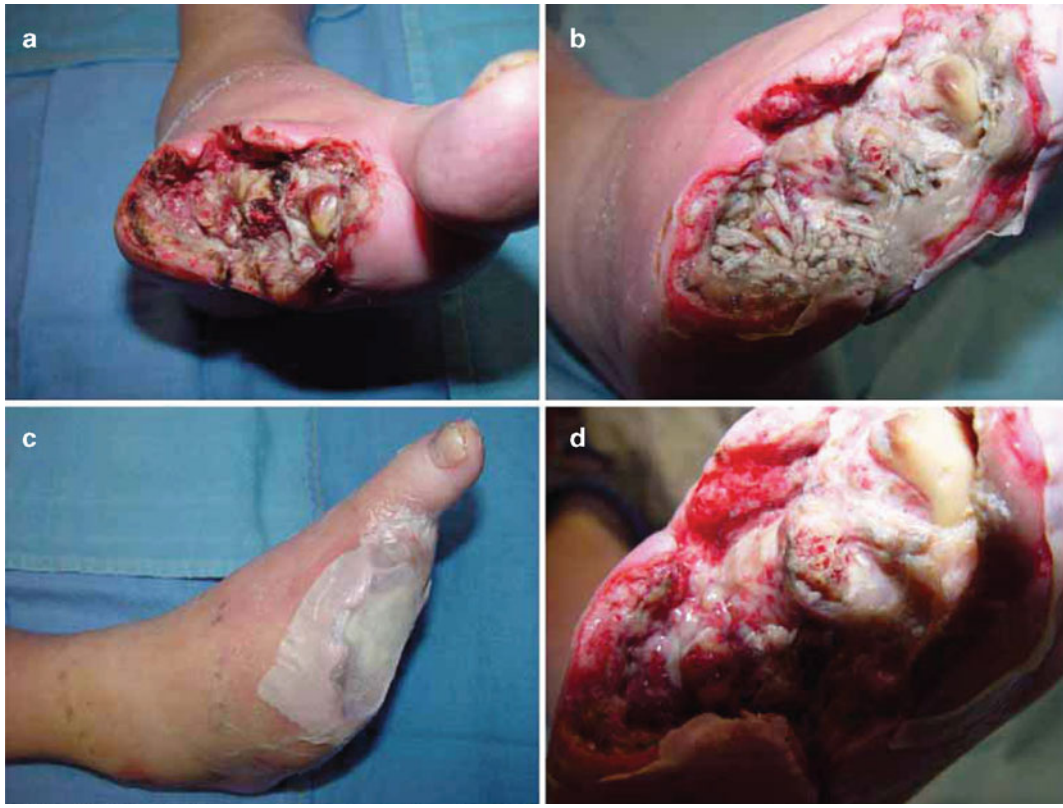

Fig. 21.6 The use of bio-surgery with maggots is an extremely effective alternative to debriding a wound when the patient cannot tolerate surgery, debridement, topical agents, or dressing changes. Maggots are the larvae of the *P. sericata* (green blow fly) and are irradiated so that they cannot metamorphose into the pupae phase. Thirty maggots consume 1 g tissue/day, consuming only necrotic tissue and bacteria and leaving any viable tissue intact. This partial necrotic forefoot (**a**) has maggots placed on it to prepare the wound for closure (**b**). The wound is sealed with a semipermeable membrane so that the maggots cannot escape (**c**). After 2 days of treatment, the wound's edge are clean and have begun to granulate (**d**)

local microcirculation has been completely interrupted and that further excision is necessary (Fig. 21.7). Only when there is normal arterial and venous bleeding at the edge of the wound can one be satisfied that the cutaneous debridement has been adequate. Healthy fat has a shiny yellow color and is soft and resilient. Dead fat has a gray pallor to it, is hard, and is not pliable. Debride fat until soft, yellow, normal-looking fat appears. Healthy fascia has a hard, white, glistening appearance. When dead, it looks dull, soft, and stringy, and is in the process of liquefying. Debride all necrotic fascia until solid, normal-looking bleeding fascia or healthy underlying fascia appears. Debriding can be simplified to serially removing tissue until one gets to normal color tissue where one sees only healthy red, white, and yellow in the wound.

Infected necrotic tendon looks dull, soft, and partially liquefied. To ensure that any hidden necrotic tendon is also removed, make a proximal and distal incision along the path of the exposed tendon (Fig. 21.8). When the extensor tendons on the dorsum of the foot become exposed, it is hard to preserve them unless they are quickly covered with healthy tissue or with neodermis and then a skin graft. With the larger Achilles or anterior tibial tendon, debride only the portion that is necrotic or infected. Leave the hard, shiny tendon underneath intact. The remaining tendon must be

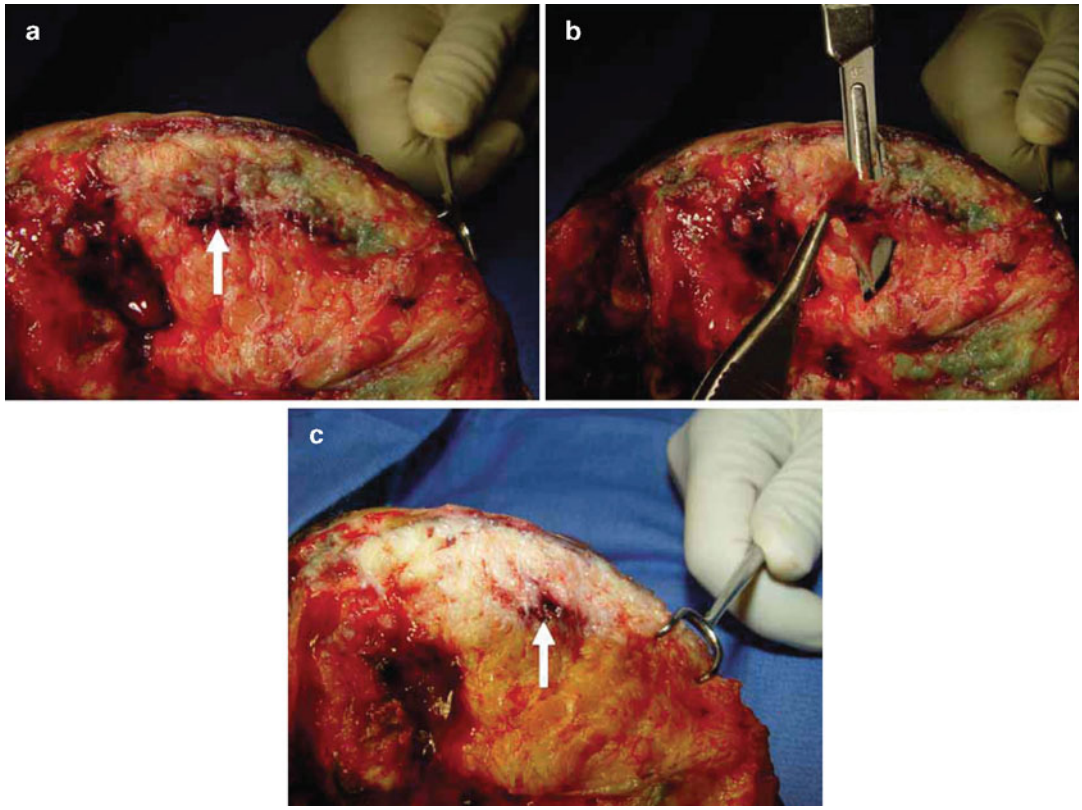

Fig. 21.7 When excising skin, look for bleeding at the normal skin edge. Clotted venules at the skin edge (**a**) indicate that the local microcirculation has been completely interrupted and that further excision is necessary. Thin slice after thin slice of the tissue containing clotted veins (**b**) should be removed until normal tissue appears (**c**). Note that in the final picture there is still a small localized area of clotted tissue that needs to be removed

kept moist and clean, as it will granulate in. The tendon can then be skin grafted. Granulation formulation can be accelerated either with negative pressure wound therapy (NPWT), with a dermal template, cultured skin substitutes, or with the combined use of topical growth factor and hyperbaric oxygen.

Healthy muscle has a bright red, shiny, and resilient appearance, and it contracts when grasped with forceps or touched with cautery. In neuropathic patients, the muscle may have a pale, possibly yellowish, color and may appear nonviable. It will have some tone, however, and will bleed when cut. Frankly dead muscle will be swollen, dull, and grainy when palpated, and it falls apart when pinched. If the muscle's viability is questionable, err on the side of caution and remove only what is not bleeding and appears dead. Subsequently, serially debride the wound until only viable muscle remains.

The key to debriding bone is to remove only what is dead and infected and leave hard bleeding bone behind. In the larger bones, use a cutting burr to remove thin layer by thin layer of bone until punctate bleeding (paprika sign) appears (Fig. 21.9). Obtain cultures of the bone remaining after debridement as well as of the debrided osteomyelitic bone to better judge the effectiveness of the debridement. If the wound is closed after all infected bone has been removed, just 1 week of appropriate antibiotics is necessary postoperatively [26]. Only when there is a question that when the bone left behind (e.g., calcaneus or tibia) may still harbor osteomyelitis, a longer course of antibiotics is required.

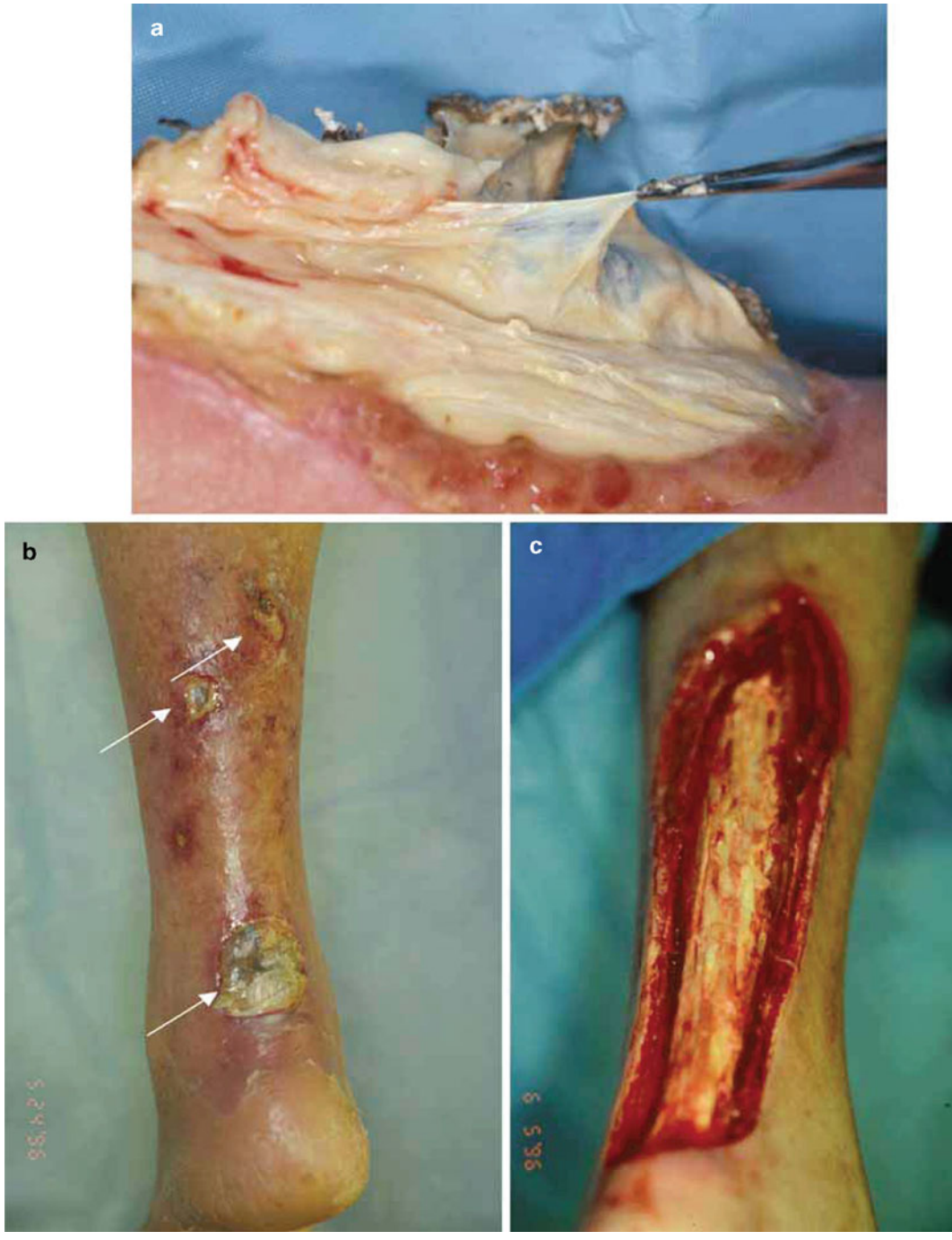

Fig. 21.8 Infected necrotic tendon looks dull, soft, and partially liquefied (**a**). It should be debrided to clean hard normal-looking tendon. For smaller tendons, it usually means loss of that tendon. However, for the necrotic Achilles or anterior tibial tendon, much of the tendon can usually be spared. Note that in picture (**b**), the lesion originated at the distal tendon and spread proximally to the mid-calf (**b**). To ensure that all necrotic tendon is removed, it is critical to explore proximal and distal to the exposed tendon to make sure that all necrotic tendon has been removed (**c**)

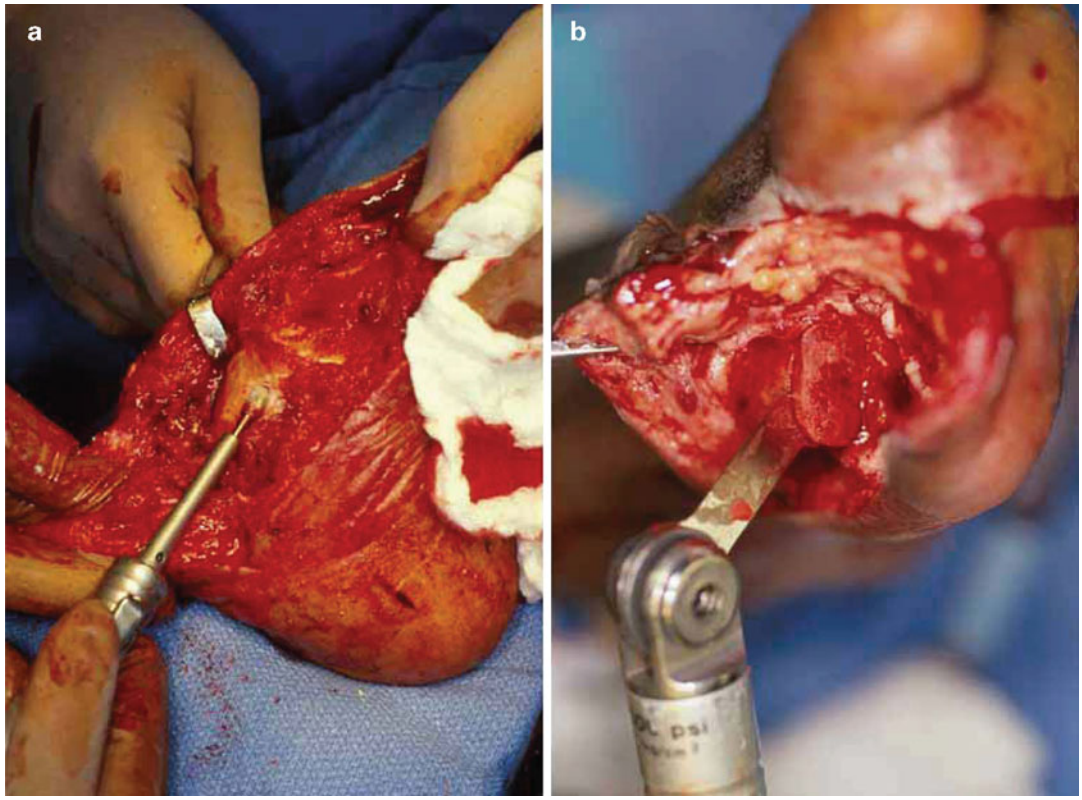

Fig. 21.9 In the larger bones, use a cutting burr to remove thin layer by thin layer of bone until punctate bleeding (paprika sign) appears (**a**). Copious irrigation is necessary to ensure that the heat generated by the burr does not damage the healthy bone The best way to debride the osteomyelitic smaller long bones (phalanx, metacarpals, or metatarsals) is to cut slices of bone serially until normal bleeding bone appears (**b**). When normal bone appears, a culture should be taken and labeled as clean bone so the surgeon and infectious disease specialist can judge whether the proximal bone is free of infection

Negative Pressure Wound Therapy

Once the wound is *clean* and *adequately vascularized*, then it can be covered with a NPWT dressing. The NPWT applies negative pressure to a wound via a closed suction mechanism [15, 27]. This speeds up the formation of granulation, sterilizes the wound, and reduces tissue edema. The mechanisms by which this occurs are poorly understood. However, it is felt that the removal of inhibitory wound healing factors, decrease in edema, increased blood flow as well as the alteration of the cellular cytoskeleton plays a role in cleaning the wound and stimulating the rapid formation of new tissue (Fig. 21.10). If the sponge is over a potential weight bearing portion of the foot (i.e., heel) a sponge bridge is attached to the site so that the drainage port is now on a non-weight bearing portion of the foot. The proximal end of the evacuation tube is then connected via a drainage canister to an adjustable vacuum pump (Fig. 21.11). The subatmospheric pressure can be applied in a constant or intermittent mode with pressures up to 125 mmHg. The intermittent mode has been found to stimulate the formation of granulation tissue more rapidly and maintain increased blood flow for longer periods of time.

If NPWT is being placed over sensitive structures such as a neurovascular bundle or a tendon, then one should place Vaseline mesh (Adaptec,© Johnson & Johnson Gateway, LLC, Piscataway, New Jersey) or silicone mesh (Mepitel,© Mölnlycke Health Care, Göteborg, Sweden)

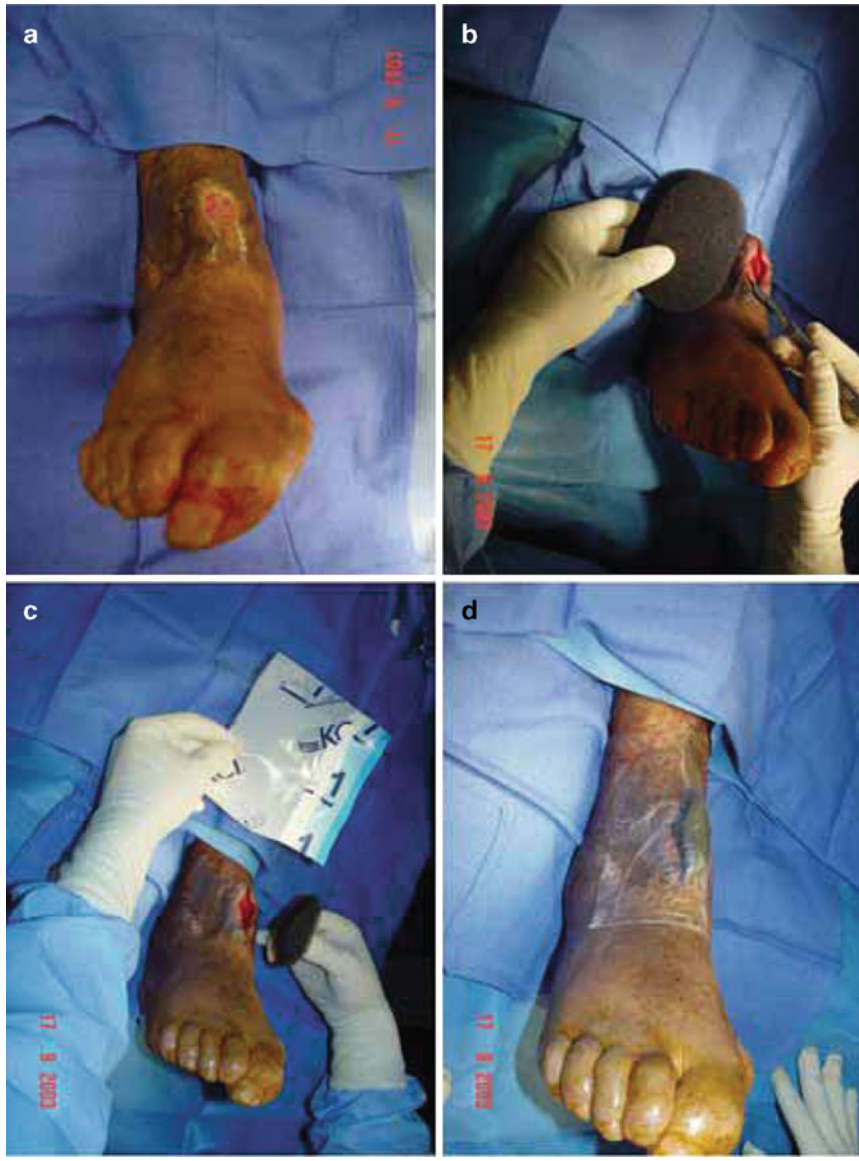

Fig. 21.10 Negative pressure therapy today come in many forms. The original commercial system (KCI, San Antonio, Texas) consists of a polyurethane ether foam sponge with pores sizes ranging from 400 to 600 μm which is placed directly on the wound surface (**a**). A scissor or scalpel blade is used to tailor the shape of the sponge to the contours of the wound (**b**). The wound, with sponge, is then covered with an impermeable adhesive drape that extends 3–5 cm over the adjacent normal skin (**c**, **d**). A small hole is made in the impermeable sheet over the sponge (**e**, **f**). The distal end of the evacuation tube is placed over the fenestration (**g**, **h**). The proximal end of the suction tubing is then connected via a drainage canister to an adjustable vacuum pump. The pump creates subatmospheric pressure that is then applied to the entire wound surface

between the wound and sponge to minimize potential damage to the underlying structure.

The quality of the granulation tissue is more vascular than that normally produced without the NPWT [28]. Small wounds can heal by secondary intention more rapidly with the NPWT. If more involved reconstruction is planned, the surgeon is no longer rushed for time to cover the

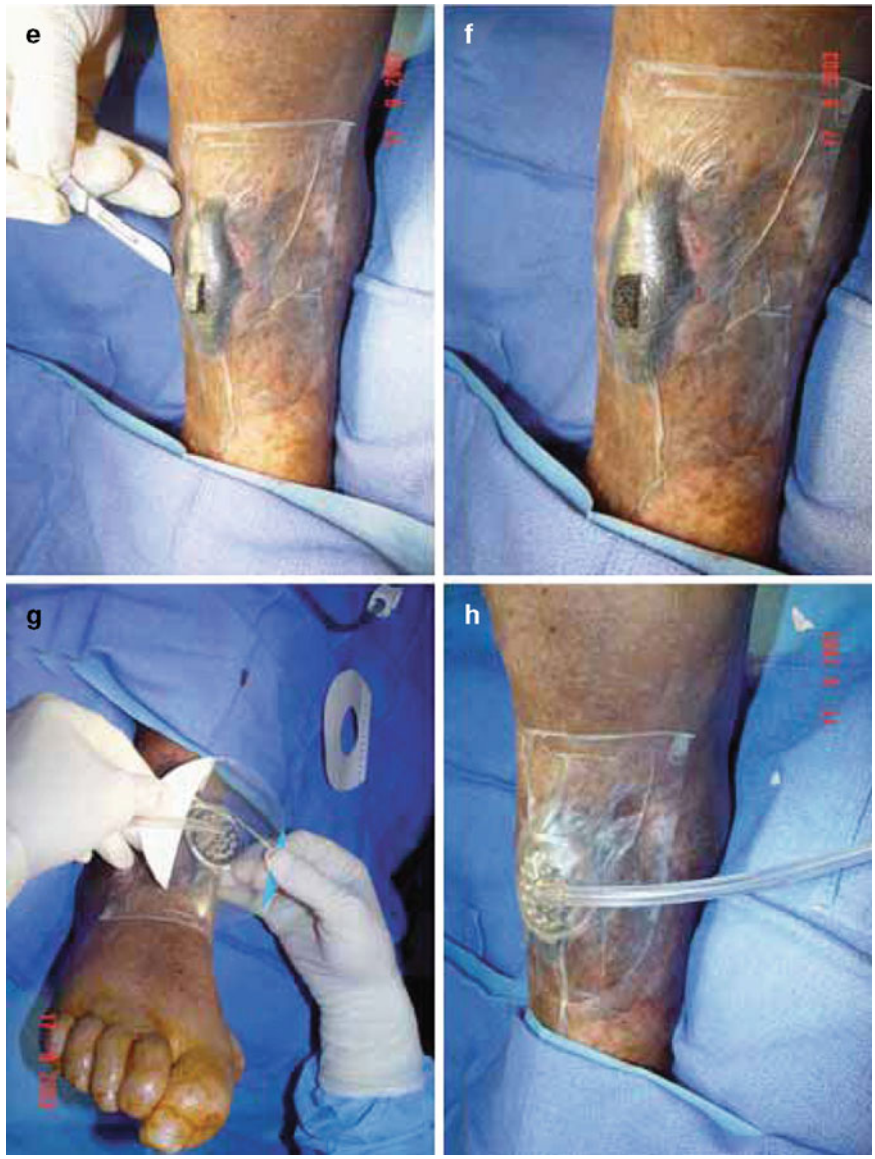

Fig. 21.10 (continued)

wound [29] with a microsurgical free flap and can electively plan the reconstruction. In addition, the reconstructive plans are usually simplified because the NPWT shrinks the size of the wound so that most wounds can be closed with a combination of local flaps and skin grafts. The NPWT has limited effectiveness if the surgeon expects it to heal a wound over an exposed fracture or joint. In those cases, the safer option is to cover the exposed joint or fracture with a local, pedicled, or free flap while the rest of the wound is skin grafted.

When Is the Wound Ready to Close?

The wound is ready to close when all the abnormal parameters surrounding the wound have been

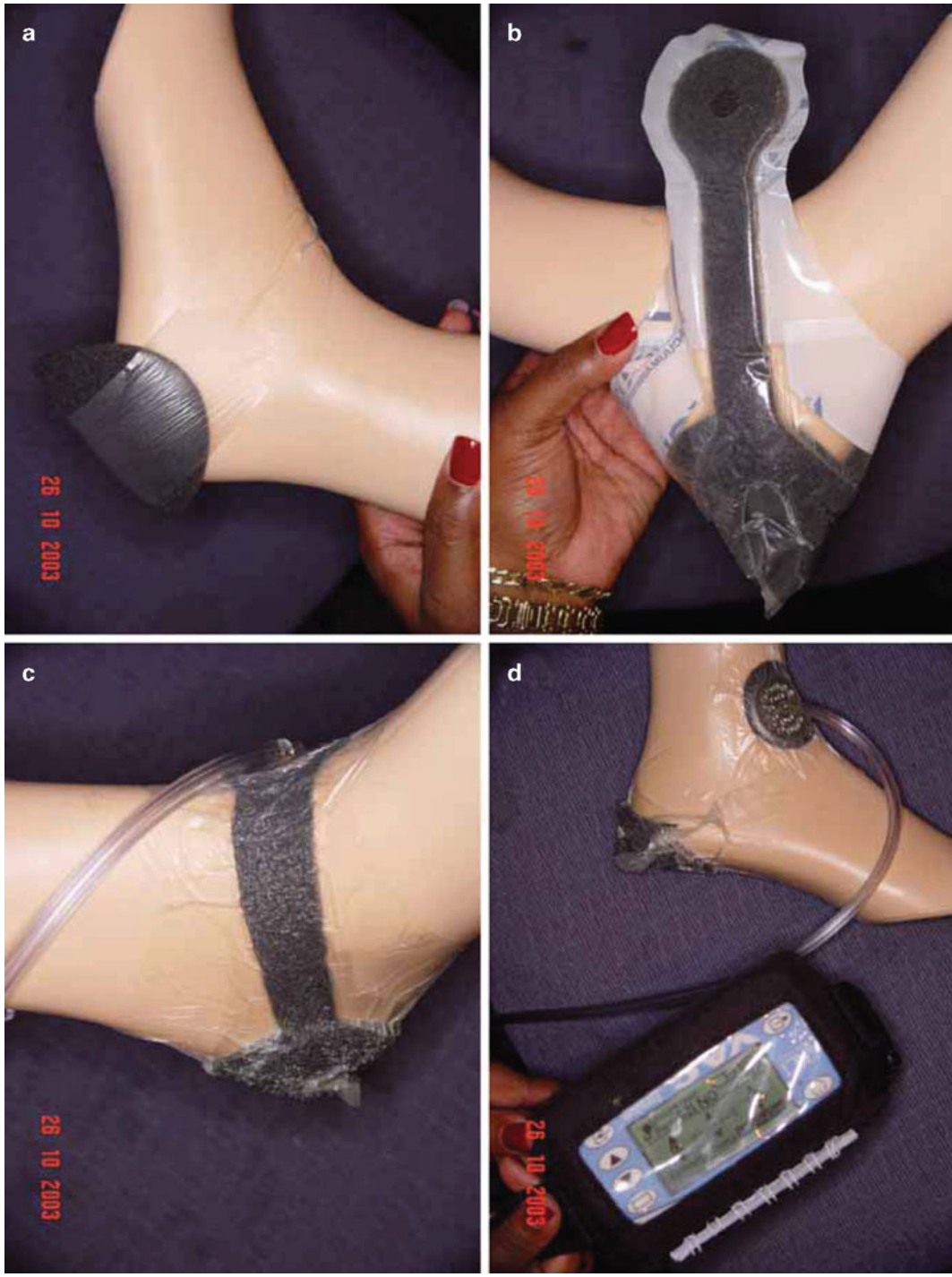

Fig. 21.11 If the sponge is over a potential weight bearing portion of the foot such as the heel (**a**), a bridge of isolated foam (**b**) is attached to the site so that the drainage port is now on a nonweight bearing portion of the foot (**c**, **d**). By surrounding the bridge with waterproof sheeting, the underlying tissue does not become macerated. The distal end of the NPWT catheter is hooked up to the portable suction device. If the patient is wearing a cam walker, the bridge can be made to be long enough to go to the thigh

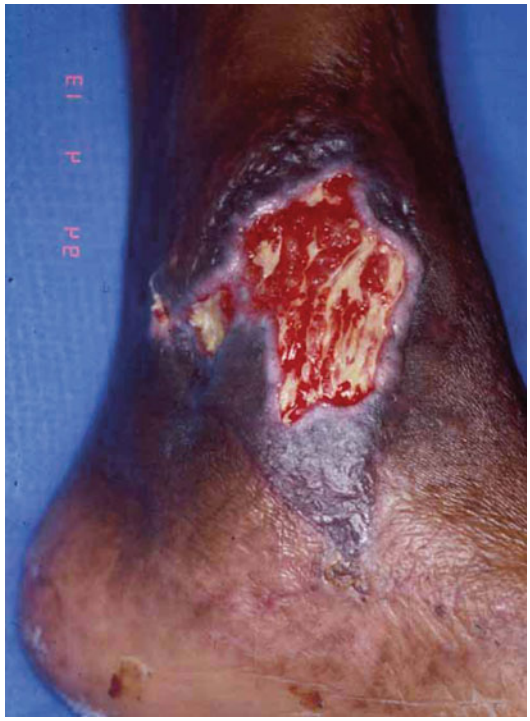

Fig. 21.12 The wound is ready to close when all signs of inflammation have disappeared: erythema, induration, and swelling. There should be wrinkled skin lines at the edge of the wound and neo-epithelialization occurring at the border of the wound. The wound can then be allowed to heal by secondary intention, closed by delayed primary closure, skin grafted, or covered with a flap

corrected and when all signs of inflammation have disappeared (Fig. 21.12). It can then be allowed to heal by secondary intention, closed by delayed primary closure, skin grafted, or covered with a flap. The wound itself should have no surrounding erythema. Cellulitis should not be confused with dependent rubor due to ischemia or recent local surgery. Wrinkled skin lines at the wound's edge are one of the most reliable signs that inflammation has largely resolved. Induration may be absent in patients who lack normal immunological response (i.e., renal failure, steroid dependence). Pain should have subsided in a wound with resolving inflammation. Decreasing pain, however, is a less reliable indicator than resolving erythema or induration. This shows that there is sufficient blood supply and a hospitable environment for the wound to go through the final stages of wound healing. The presence of new epithelium at the wounds edge reflects a healthy wound that is on its way to healing by secondary intention. If quantitative counts are available, then a count of less than 10^5 bacteria per gram of tissue signifies that the wound is ready to successfully be skin grafted [30]. Alternatively, if an allograft or xenograft placed on the wound takes, then the wound bed is sterile enough for a skin graft to take.

Closure Techniques

Closure techniques include allowing the wound to heal by secondary intention or by closing it with (1) delayed primary closure, (2) skin graft, (3) local flap, (4) pedicled flap, (5) free flap. If surgical closure is chosen, there should be two setups of instruments in the operating room: one for the debridement and one for closure. This is to avoid contaminating the just debrided wounds with instruments that were used to debride it.

Promoting Healing by Secondary Intention

A healthy granulating wound normally decreases in surface area by at least 10–15% per week [31]. The biomechanical abnormality that caused the wound should be addressed. If the wound is on the plantar forefoot and the etiology is an equinovarus deformity from a tight Achilles tendon and/or a hammer toe, the Achilles tendon should be lengthened and/or the hammer toe corrected. The plantar foot should then be un-weighted. If the wound is located near a joint surface (i.e., ankle), the involved joint should be immobilized by a splint or external fixator to prevent shear forces from disrupting the ongoing repair. A moist dressing on the wound allows for more rapid epithelialization of the wound [32]. If the wound fails to respond to the above conservative measures, healing adjuncts should be implemented.

When dealing with wound healing adjuncts, it is important to keep their cost in mind. Xenograft costs approximately $50 per role of 400 cm^2,

growth factor $400 to $500 per 15 g, and cultured skin derivatives $1,500 per 25 cm^2 of tissue. Application of the NPWT is approximately $125 per day while hyperbaric oxygen costs in excess of $500 per day. In order to accurately estimate the total cost of a given option, one also has to factor in the cost of visiting nurses, hospital stay, and operative costs. Whenever clinically applicable, one should first start with the least expensive and move up the ladder when a given treatment fails to bring about the desired results.

(a) *Platelet-derived growth factor*: This gel has been shown effective in diabetic wounds when they are well vascularized, clean, and regularly debrided [33]. Removing the proteinaceous coagulum from the wound surface before applying the growth factor is important because the coagulum contains metalloproteases that will digest the applied growth factor before the latter can affect the wound. Patients are given scrub brushes or soft toothbrushes and are instructed to scrub the wound surface every time before applying the growth factor.

(b) *Temporary coverage*: Xenograft (pigskin) [34] or allograft (cadaver skin) [35] provides an excellent temporary dressing over clean healthy wounds. They are an excellent temporary dressing that provides a collagen-based scaffolding for new tissue to grow into. If the temporary graft initially "takes", it turns pink indicating that the underlying bed is sterile and well enough vascularized for a split-thickness skin graft to successfully take. In healthy patients, rejection starts at approximately 7–9 days. In the immune compromised patient, it can take up to a month before the temporary skin graft is rejected.

(c) *Cultured skin substitutes*: While these are not skin graft substitutes per se, they are bioengineered skin equivalents that provide a moist living surface producing an entire array of local growth factors to the underlying wound bed. They are made by allowing live human fibroblasts to migrate into and populate the collagen scaffolding. This scaffolding can then be covered with a layer of epidermis grown separately. These products come in two commercial forms: combined dermal-epidermal graft (Apligraf,© Organogenesis Inc. Canton, MA, USA) or a dermal graft (Dermagraft,© Smith & Nephew, Hull, UK). They have been show to be effective in healing both venous stasis ulcers [36, 37] and diabetic ulcers [38, 39].

(d) *Hyperbaric oxygen*: Hyperbaric oxygen supplies the body with oxygen at two to three times normal atmospheric pressures. Hyperbaric oxygen saturates existing hemoglobin and dissolves sufficient free oxygen in the blood plasma to increase the concentration of oxygen at the wounds edge. The increase of oxygen at the wound's edge significantly increases the oxygen gradient between the edge and the hypoxic center of the wound bed. The higher the gradient, the stronger the body's wound healing response [40, 41] and more rapid the promotion of angiogenesis, collagen synthesis, and neo-epithelialization. In addition, hyperbaric oxygen potentiates the white blood cells ability to destroy bacteria [42]. Hyperbaric oxygen is most effective if there is adequate vascular inflow. Before undergoing hyperbaric oxygen treatment, candidates should undergo an oxygen challenge test to see whether there is a rise in the local tissue oxygen pressure after exposing the lungs to increased oxygen content. Breathing in 100% oxygen should lead to at least a 10 mmHg rise in tissue oxygen levels around the wound site. Diving in a chamber at two atmospheres should increase the tissue oxygen level to above 300 mmHg. Otherwise, the hyperbaric oxygen treatments unlikely to be effective.

Combining platelet-derived growth factor with hyperbaric oxygen treatments is more effective together than either treatment alone (Fig. 21.13) [43]. Therefore, if the clinical decision is to begin hyperbaric oxygen therapy to stimulate wound healing, growth factor should probably be applied to the wound at the same time to maximize the benefits of hyperbaric oxygen. Many wound healing adjuncts have level 2 evidence of their effectiveness in healing diabetic foot wounds [44]. The use of NPWT to prepare

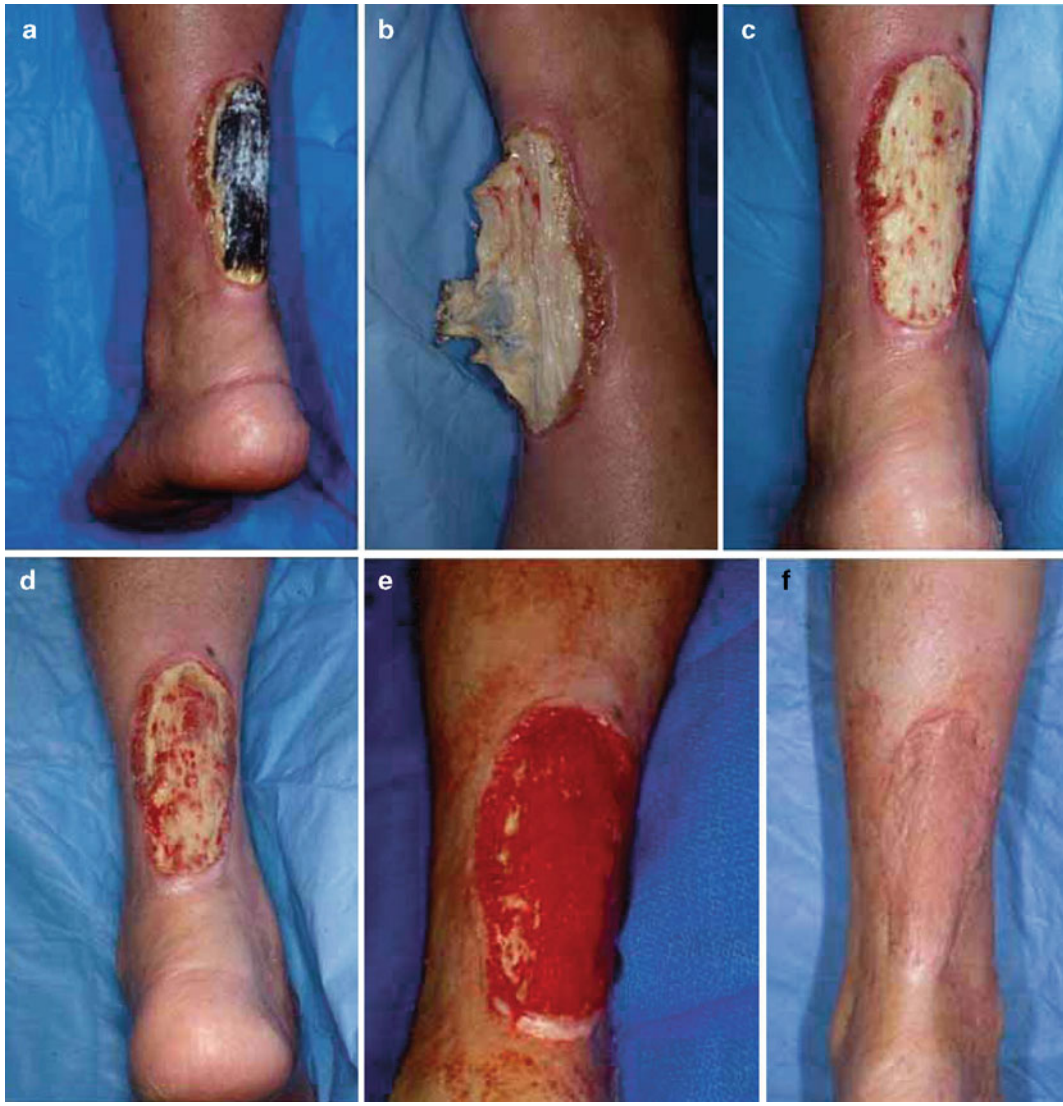

Fig. 21.13 This elderly diabetic patient presented with gangrene of the Achilles tendon (**a**). The wound was debrided by removing the loose filmy and necrotic portions of the tendon (**b**). With both the posterior tibial and peroneal artery open, there was enough blood flow to the tendon to allow it to heal once the infected portion was removed. The wound was then treated with the combination of hyperbaric oxygen and topical growth factor. Granulation appeared at week 1 (**c**), increased at week 2 (**d**), and covered the entire week by week 3 (**e**). The wound was then skin grafted and the patient survived an additional 2 years without problems (**f**)

debrided diabetic foot wounds has been shown to hasten healing and decrease amputation rates [45]. The use of biologically active wound coverage has also been shown to speed up healing (Regranex, Apligraf and Dermagraft) [46–49]. Although the use of hyperbaric oxygen therapy remains somewhat controversial, there is now level one evidence that it has been shown to decrease amputation rates and hasten healing [50, 51]. These should all be considered in concert with any of the above discussed reconstructive strategies.

Closing a Wound by Delayed Primary Closure

Closing with monofilament vertical mattress sutures creates good tissue eversion along the wound's edge without requiring deeper sutures. Interrupted suture closure gives the surgeon more option when addressing a seroma or hematoma. Removal of one or two of the overlying sutures rather than opening the entire closure is usually sufficient to adequately drain the underlying seroma or hematoma. However, if deeper infection is suspected, the wound should be fully explored (Fig. 21.14). No deep sutures should be used as they potentiate infection and give any residual biofilm a chance to reestablish itself in the wound.

Often the skin edges are too far apart to close primarily (i.e., postfasciotomy, postfracture). Gradual re-approximation of the skin edges is possible by serial operations every 2–3 days where the skin edges are approximated up to the point of blanching with horizontal mattress sutures. NPWT can be placed over the remaining soft tissue gap to help decrease the edema and make the surrounding tissue more mobile. Alternatively, skin staples can be placed at the wound edges and a vessel loop is threaded through them much like tying up shoe laces [52]. The band is tightened daily until the edges touch and then the wound can be allowed to heal by secondary intention or formally closed using vertical mattress sutures. Finally, Dermaclose (Wound Care Technologies, Chanhassen, Minnesota) applies continuous tension on the wound edges via a spring-like mechanism which gradually approximates wound edges.

Skin Graft

This is the simplest of all coverage techniques with the only prerequisite being a wound with a bed of healthy granulation tissue. The superficial layer of granulation tissue is removed to ensure that there is minimal bacterial contamination/biofilm within the interstices of the granulation buds. The use of the Versa Jet© in this setting is ideal because one can precisely adjust the depth of debridement and rapidly establish a smooth and level recipient bed. The wound is then redraped and clean instruments are used.

Preferable donor sites include the ipsilateral thigh, leg, or instep. The size of the defect is measured to determine the amount of skin graft needed. The area needed is then drawn on the donor site. The appropriate width skin graft guide (1″, 2″, 3″, or 4″) should be used to harvest the appropriate size skin graft. The thickness of the harvest is set at 15/1,000 of an inch which is an effective compromise between adequate take rate and skin graft contraction [53].

To prevent shearing forces from disrupting the graft, a bolster can be tied over the graft. For a bolster dressing, monofilament ties are placed at the edge of the wound and tied over the sponge and placed over skin graft. The bolster dressing is removed 7–10 days later (Fig. 21.15).

NPWT is an alternative method of covering fresh skin grafts and provides successful skin graft take rates of as high as 95% [17, 54]. NPWT facilitates maximal contact between the skin graft and the bed, helps stabilizes the skin graft on the bed to counteract shear forces, and removes any excess fluid that could disrupt the contact between the graft and the underlying bed (Fig. 21.16). NPWT has been more effective than a bolster dressing in ensuring high initial skin graft take [55]. The fresh skin graft is first covered with a nonadherent dressing (silicone or Vaseline mesh). A sheet of silver ions can then interposed between the mesh and VAC sponge to ensure better bacterial control. The VAC sponge is then placed on top and continuous pressure is applied for 3–5 days postoperatively.

When considering skin grafting over bone, tendon, or joint, creating a neodermis improves the chances of skin graft flexibility and durability. Integra® artificial dermis (Integra LifeSciences Holding Company, Plainsboro, New Jersey) is composed of an overlying removable silicone film (to prevent desiccation) with an underlying dermal matrix of cross-linked bovine collagen

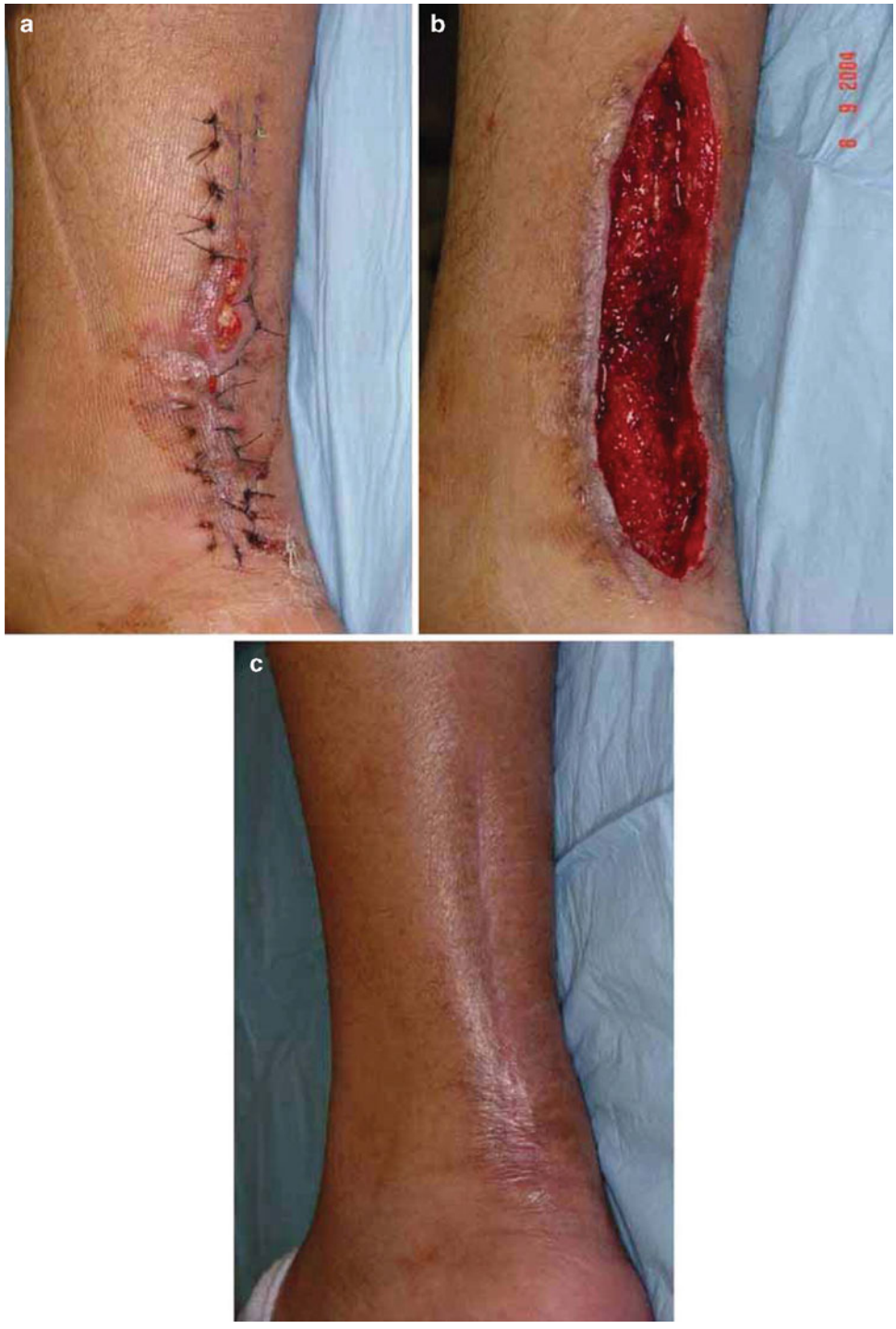

Fig. 21.14 This patient presented with an infected Achilles tendon repair (**a**). The wound was opened, the tendon debrided, and the infected Ethibond suture removed. NPWT was placed on the wound until the cultures were back (**b**). NPWT decrease the edema and the wound could be closed primarily. To minimize the risk of re-infection, no deep sutures were used and simple vertical mattress suture with monofilament suture were used (**c**)

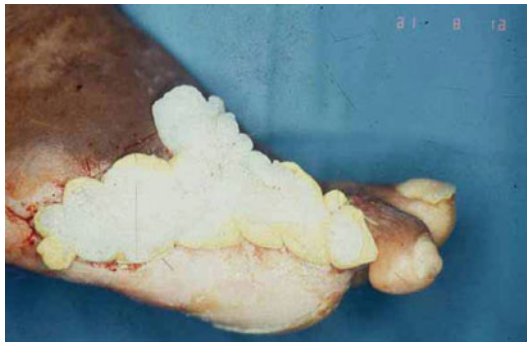

Fig. 21.15 To prevent shearing forces from disrupting the graft, a bolster can be tied over the graft. Bolster stitches are placed around the graft by going through the edge of the skin graft and wound bed, tying the suture, and leaving one end long enough to then tie over the bolster. Vaseline gauze is then placed on the graft and wet unwrung cotton balls are placed on top of the gauze. The long ties are then tightly tied over the cotton balls, which wrings out excess fluid as the cotton balls conform to the underlying recipient bed. The result is application of uniform pressure over the entire skin graft. The bolster dressing is removed 7–10 days later

and chondroitin sulfate [56–58]. The dermal layer functions as a dermal template to facilitate the migration of the patient's own fibroblasts, macrophages, lymphocytes, and endothelial cells as well as new vessels. The sheet of Integra is meshed, cut to fit the wound, and affixed to the site with staples or suture. Over the ensuing week(s), a new cell populated dermis is formed. The revascularization process is accelerated two- to threefold by placing NPWT over Integra [59]. Then, the silicone layer can be removed so that a thinner skin autologous skin graft (8/1,000″ to 10/1,000″) can be placed on it (Fig. 21.17).

For heel wounds, the Ilizarov frame is very useful because it not only immobilizes the ankle but it also suspends the foot in mid air so that the patient cannot disrupt the graft (Fig. 21.18). If the graft is on the plantar aspect of the foot, there should be no weight bearing until the skin graft has matured (usually 6 weeks). For wounds on

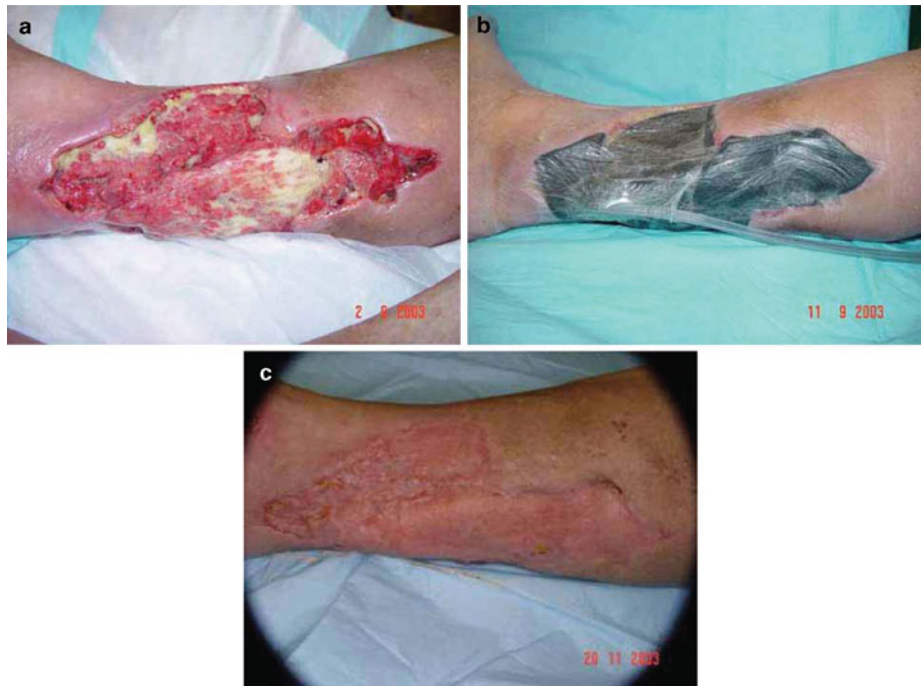

Fig. 21.16 NPWT facilitates maximal contact between the skin graft and the bed (**a**), helps stabilizes the skin graft on the bed to counteract shear forces while removing any excess fluid. The fresh skin graft is first covered with a nonadherent dressing (silicone or Vaseline mesh). A sheet of silver ions can then interposed between the mesh and NPWT to ensure better bacterial control. The NPWT sponge is then placed on top (**b**) and continuous pressure is applied for 3–5 days postoperatively. The graft is then allowed to fully heal with a simple semiocclusive dressing such as Vaseline gauze (**c**)

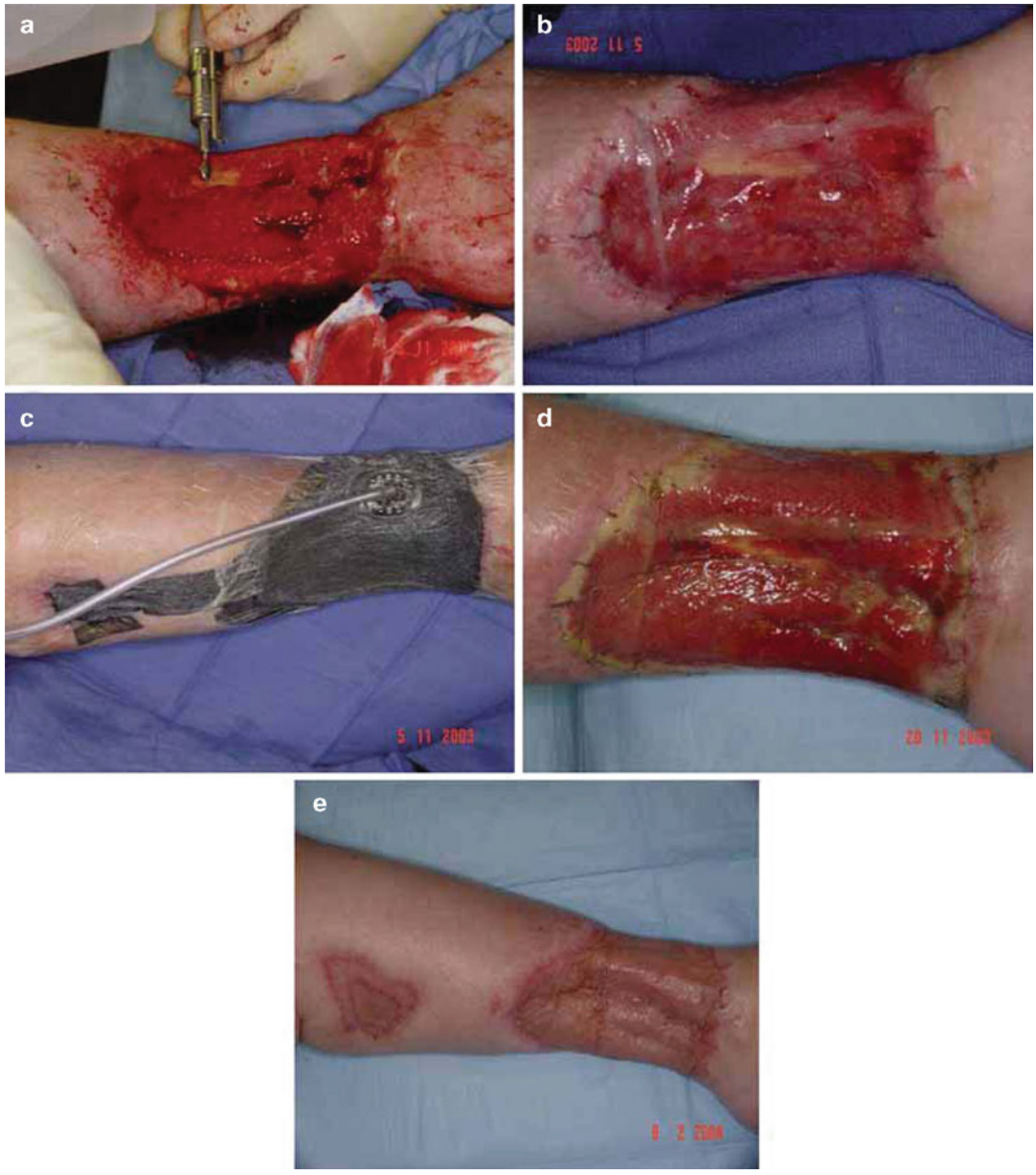

Fig. 21.17 This diabetic patient had exposed tibia and large almost circumferential wound just above the ankle (**a**). The sheet of neodermis is meshed, cut to fit the wound, and affixed to the site with staples or suture (**b**). NPWT is placed over the neodermis to speed up the vascularization of the dermal template (**c**). Once that has occurred (**d**), the silicone layer can be removed so that a thin skin autologous skin graft (8/1,000″ to 10/1,000″) can be placed on it. The skin graft is covered with silicone mesh and NPWT for 3–5 days and then a normal dressing is placed on the graft as it continues to heal (**e**)

the weight bearing portions of the foot (heel, lateral midfoot, under the metatarsal heads), plantar glabrous skin grafts are the ideal source of autographs because they permit the regeneration of the normal glabrous plantar surface [60].

Local Flaps

Local flaps are flaps with unidentified blood supply adjacent to a given defect that are either rotated on a pivot point or advanced forward to

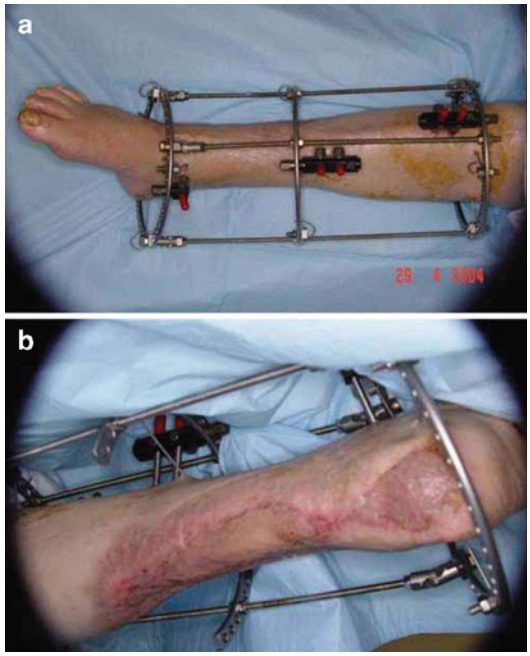

Fig. 21.18 For heel ulcers, the Ilizarov frame is very useful because suspends the foot in midair so that the patient cannot disrupt the graft during the healing process. The Ilizarov can also stabilize the ankle in neutral position to avoid the development of equino-varus deformity

cover the defect. They come in various shapes (square, rectangular, rhomboid, semicircular, or bilobed) [61]. They usually consist of skin and the underlying fat or skin, fat, and the underlying fascia. They, however, can also include the muscle. It is important to carefully pre-plan the flap by first accurately determining the size of the defect after debridement. The flap should be designed in the area where the tissue is mostly mobile. Using a template when designing the flap and holding its base at the pivot point as it is being swung into the defect is the best way of estimating the adequateness of the design. The ratio of length to width is critical for the survival of the tip of the flap [62]. Because the blood flow to the skin in the foot and ankle is not as developed as in the face, the length to width ratio should not exceed a 1:1 or 1:1.5 ratio. The viability of such a flap is increased when one can Doppler out a cutaneous perforator at the base of the planned flap. To ensure adequate tension-free coverage, a slightly larger pattern should be used than what would anatomically be necessary. When moving the flap to cover the defect, it is important that the flap fill the defect without tension to avoid compromising the blood flow to its distal end. A force [63] of 25 mmHg causes enough venous congestion for flap necrosis unless the tension is released within 4 h.

Local flaps are very useful in coverage of foot and ankle wounds because *they only need to be of sufficient size to cover the exposed tendon, bone, or joint*. The rest of the wound can then be covered with a simple skin graft. This combination of limited local flap and skin graft frequently obviates the need of larger pedicled or free flaps. If correctly designed, a local flap can also improve the surgical exposure of the underlying tissue if corrective surgery has to be performed [64]. The harvesting of an appropriately designed flap often improves the exposure of joints, bone, or tendons sufficiently to avoid making an extra incision. In addition, local flaps are a very useful mode of reconstruction when trying to close a wound through an Ilizarov type fixator. This is because the frame often makes it impossible to perform the extensive dissection required for pedicled flaps or to provide the necessary space to perform the microsurgical anastomosis for free flaps.

Flaps that Rotate Around a Pivot Point

These random flaps rotate around a single pivot point and therefore need to be planned carefully to avoid excessive tension along the radius of the arc of rotation. The *rotation flap* is designed when a pie-shaped triangular defect is created to remove a lesion or preexistent defect. The base of the triangle lies along the hypothetical circumference of a semicircular flap that can then be rotated into the defect. The most useful application of this type flap is on the plantar aspect of the foot where the flap is elevated off the plantar fascia and rotated in position. It can also be used over the plantar forefoot (Fig. 21.19), at both malleoli and on the dorsum of the foot [65, 66]. If vascular anatomical considerations dictate, the flap can also include underlying fascia and/or muscle.

Transposition flaps are rectangular flaps that can be rotated up to 90°. The end of the flap has

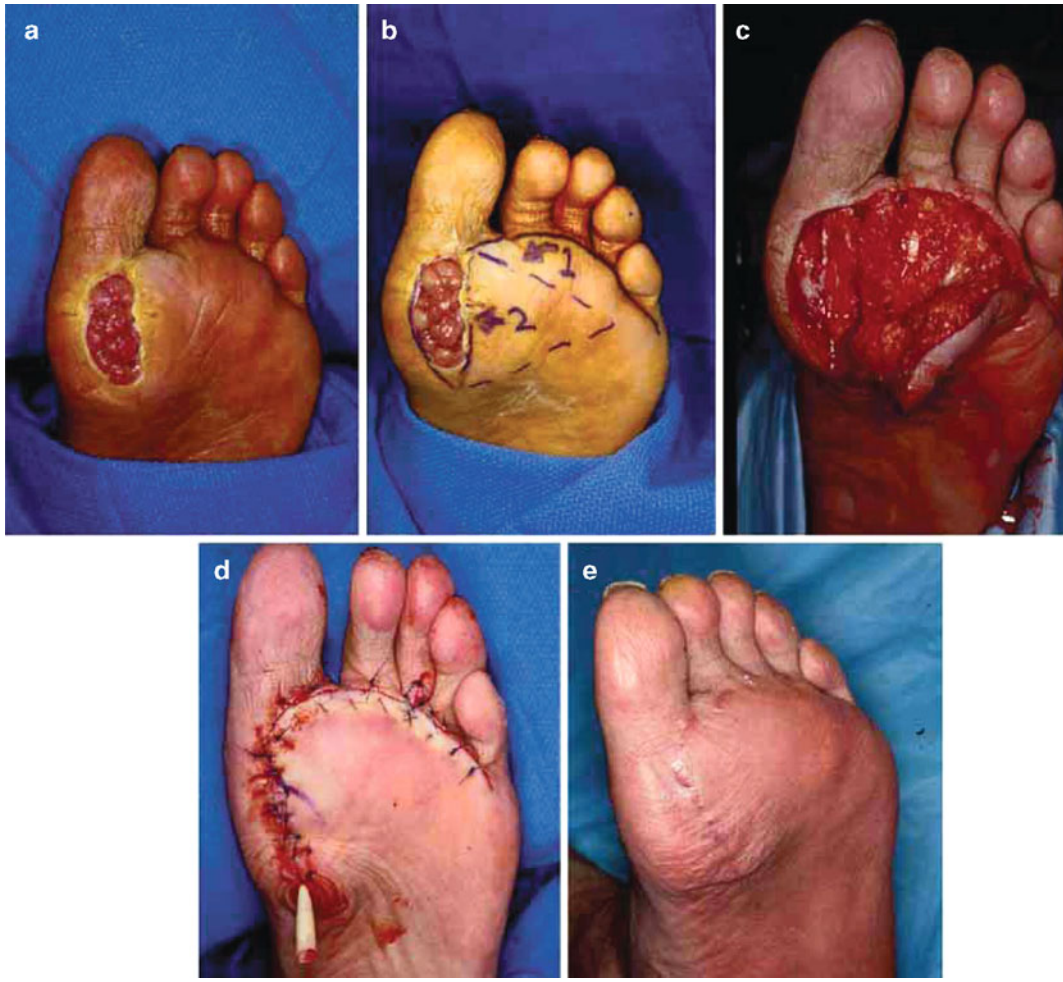

Fig. 21.19 This is a morbidly obese diabetic with an ulcer under the first MTP (**a**). Potential flaps for closure included a rotation flap and a V–Y advancement flap (**b**). The wound was debrided and a rotation flap was chosen as the mode of reconstruction. The flap was elevated with great care to preserve the neurovascular bundles to the toes (**c**). The flap is sewn into position with biased stitches to prevent tension on the distal end of the flap (**d**). The flap went on to heal despite poor compliance in keeping weight off the foot during the healing phase (**e**)

to be longer than the distance between the pivot point and the edge of the defect so that when the flap is rotated, it can fit in without tension. Preplanning the rotation with gauze or paper is the key to avoiding excessive tension on the distal end of the flap at inset. The donor site can usually be closed primarily. Otherwise, it may require skin grafting. The dog ear that results from rotating the flap should not be addressed at the initial surgery. The dog ear will usually flatten down. This is the most frequently used flap to cover the malleoli or exposed tibial-talar fusion around an Ilizarov frame (Fig. 21.20).

Advancement Flaps

Advancement flaps are moved directly forward to fill a defect without rotation or lateral movement. A rectangle of skin is dissected out and should include, at a minimum, skin and subcutaneous tissue. The flap is advanced into the defect. This may create a folding of the tissue at both ends of its base (burrow's triangles) which can be

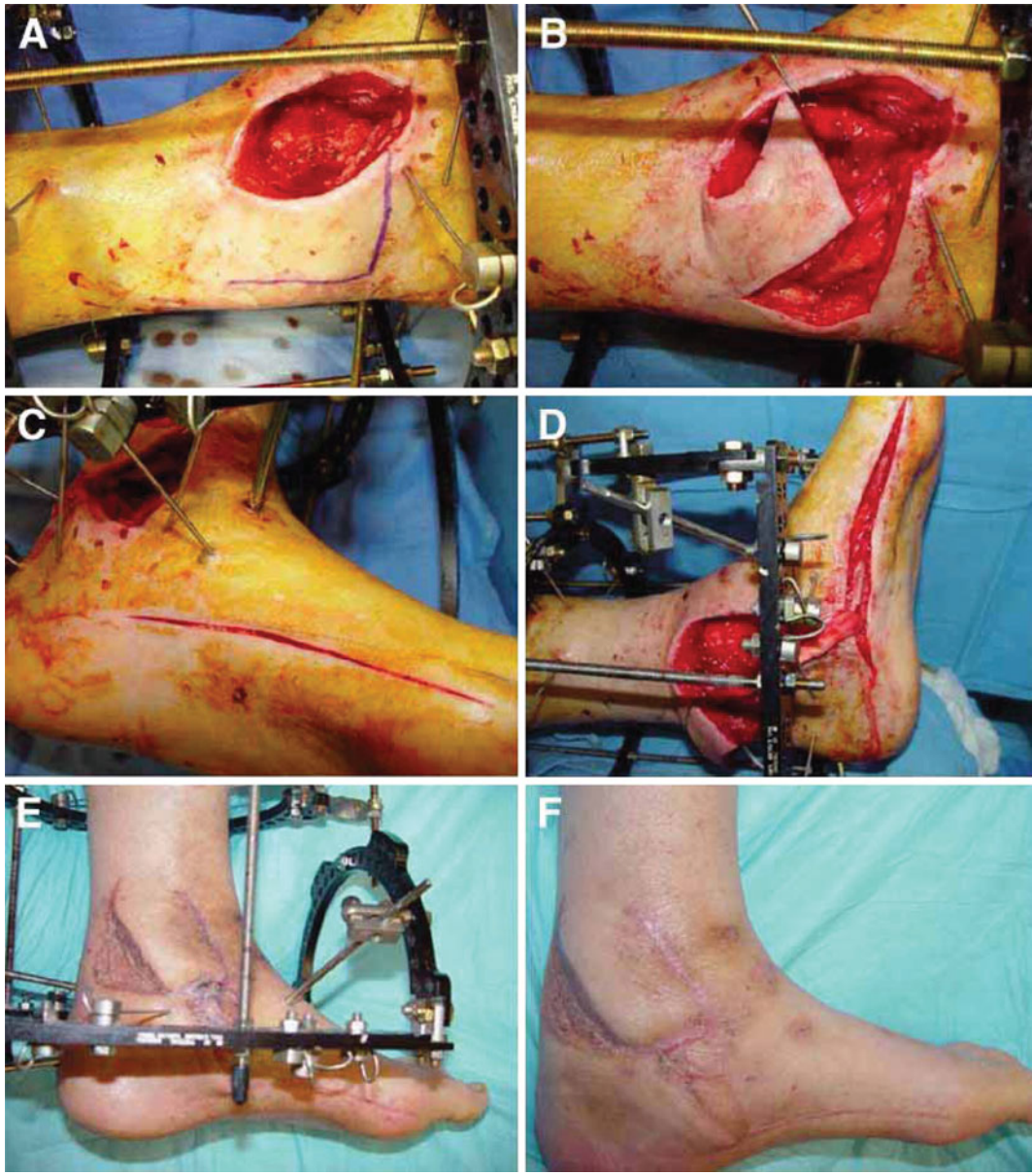

Fig. 21.20 This patient developed an infected Charcot ankle joint. The infected tibio-talar joint was resected and the remaining foot and ankle were stabilized using an Ilizarov frame (**a**). The defect was debrided and the upper half of the exposed joint was covered with a local transposition flap (**b**) while the distal portion of the defect was covered with an abductor Hallucis muscle flap and skin graft (**c**, **d**). The wound went on to heal without incident (**e**, **f**)

removed so that the skin can be sutured together without causing any irregularities in the contour. It is also important that the tension on the flap is adjusted so that there is no blanched area when it is in its new position.

A *V–Y flap* is a "V"-shaped flap that, when advanced, forms a "Y" (Fig. 21.21). The V–Y flap depends on direct underlying perforators to stay alive. For that reason, NO undermining whatsoever can be done when dissecting out this

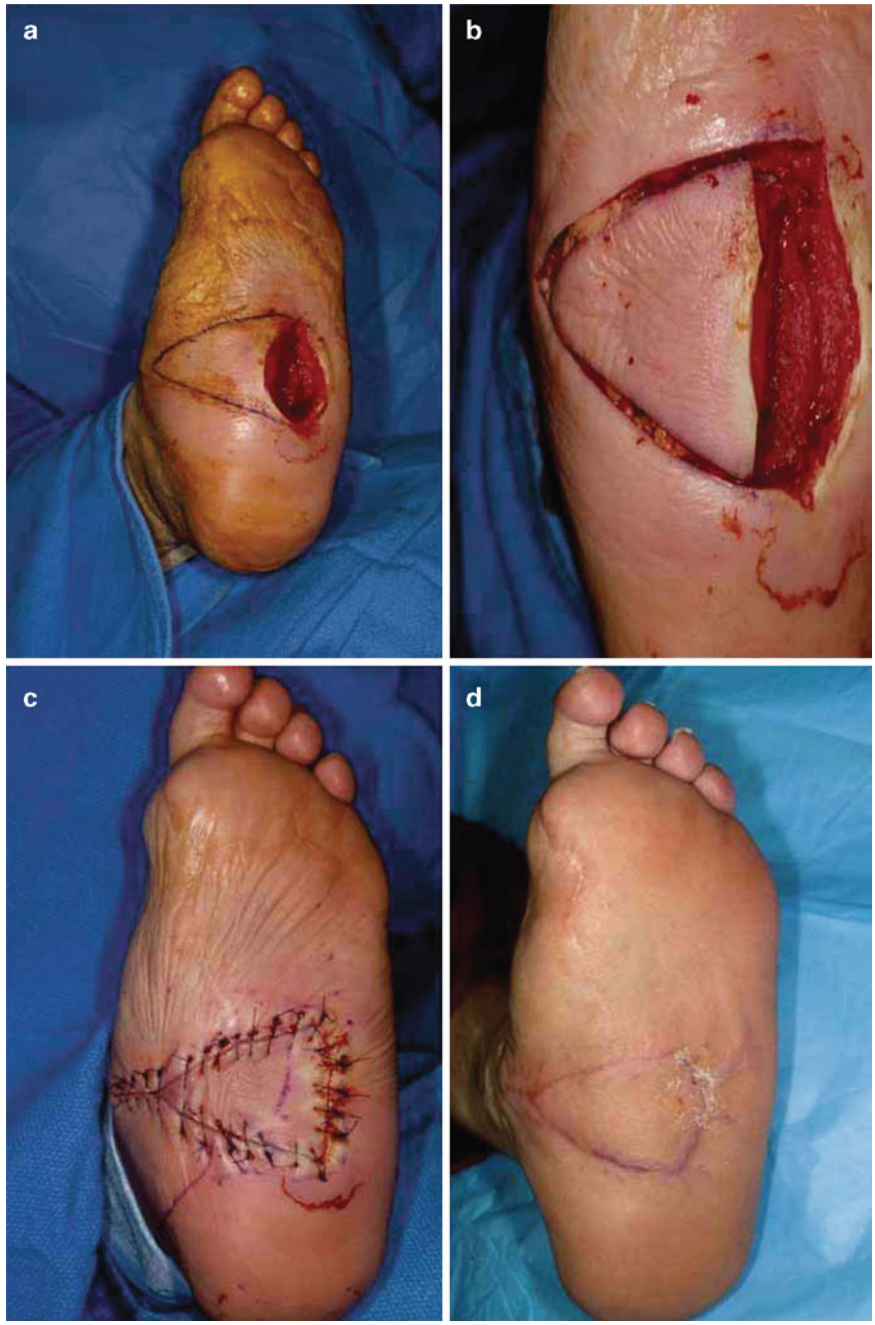

Fig. 21.21 A *V–Y flap* is a "V" shaped flap (**a**, **b**) that, when advanced, forms a "Y". The V–Y flap depends on direct underlying perforators to stay alive. For that reason, no undermining whatsoever can be done when dissecting out this flap. On the plantar aspect of the foot, the maximum advancement is limited to 1–2 cm

flap. It is important to realize that the maximum advancement is limited to 1–2 cm. Therefore, if the defect is larger, double opposing V–Y flaps can be used to close defects of up to 3–4 cm. wide. The flap is especially useful for defects on the sole of the foot [67]. To advance the flap adequately, one has to cut through the plantar fascia on both side of the triangle of tissue to be

advanced. The flap should be designed as large as possible to ensure the inclusion of as many perforators as possible.

Pedicled Flaps

Pedicled flaps have identifiable blood vessels feeding the flap. They can contain various tissue combinations including cutaneous, fasciocutaneous, muscle, musculo-cutaneous, osteo-cutaneous, osteo-musculo-cutaneous type flaps, etc. These flaps work well if they were not involved in the initial trauma, infection, or radiation field. Otherwise, the flaps are stiff, difficult to dissect out, and difficult to transfer. In addition, the flap has to be soft and pliable because the vascular pedicle is usually intolerant of any twisting or turning that occurs when the flap is swung into its new position.

These flaps are often more difficult to dissect and have a higher complication rate than performing a free flap that can run as high as 30–40% [68]. Harvesting a pedicled flap often leaves a donor site deficit on the foot and ankle that has to be skin grafted. However, pedicled flaps allow the surgeon to perform a rapid operation with a short hospital stay that yields excellent long lasting results. The anatomy and techniques of dissection are discussed above and in flap anatomy books [69, 70]. It is important to practice these flap on cadaver legs as the dissections are often tedious and can be difficult. The distal reach of the flap often provides insufficient tissue so that it is very important to understand the size limitations of each flap.

Lower Leg and Ankle: Muscle Flaps

The lower leg muscles are poor candidates for pedicled flaps because most of them are type 4 muscle with segmental minor pedicles as their blood supply and therefore only a small portion of the muscle can safely be transferred. The distal portion of some of these muscles can be used to cover small defects around the ankle medially, anteriorly, laterally [71]. For small and proximal defect, the muscle flap can usually be separated from its distal tendon to minimize the loss of function.

The Extensor Hallucis Longus m. (*anterior tibial artery*) can cover small defects that are as distal as 2 cm above the medial malleolus. The Extensor Digitorum Longus m. and Peroneus Tertius m. (*anterior tibial artery*) are used for small defects as distal as 2.1 cm above the medial malleolus. The Peroneus Brevis m. (*peroneal artery*) can be used for small defects as distal as 4 cm above the medial malleolus. The Flexor Digitorum Longus m. (*posterior tibial artery*) can be used for small defects as distal as 6 cm above the medial malleolus. The Soleus muscle (*popliteal*, *peroneal*, and *posterior tibial artery*) is the only type 2 muscle in the distal lower leg where the minor distal pedicles can be safely detached and the muscle with its intact proximal major pedicles can be rotated to cover large (10×8 cm) anterior lower leg defects as distal as 6.6 cm above the medial malleolus. It can be harvested as a hemi-soleus for small defects [72] and as an entire soleus for larger defects. All the just described muscles usually have to be skin grafted for complete coverage. In addition, the ankle has to be immobilized to avoid dehiscence and ensure adequate skin graft take. The use of external frames can be very useful with the former and the use of the NPWT device for the latter.

If a larger flap or wider angle of rotation is needed, one of the three major lower leg arteries with the relevant minor perforators has to be taken with the muscle flap. The sacrifice of a major artery should only be considered if all three arteries are open and there is excellent retrograde flow. These flaps are usually harvested distally and therefore the accompanying artery depends on retrograde flow. Because these flaps are larger, the tendon is also taken with the muscle. It is therefore important to tenodese the distal portion of the severed tendon to the tendon of a similar muscle so that the function is not lost. For example, if the distal Extensor Hallucis Longus (EHL) muscle is harvested, the EHL tendon distal to the harvest should be tenodesed to the Extensor Digitorum Longus (EDL) so that the hallux maintains its position during gait (Fig. 21.22). Because the loss of the anterior tibial tendon is so debilitating, the distal muscle should not be harvested unless the ankle has been or is being fused.

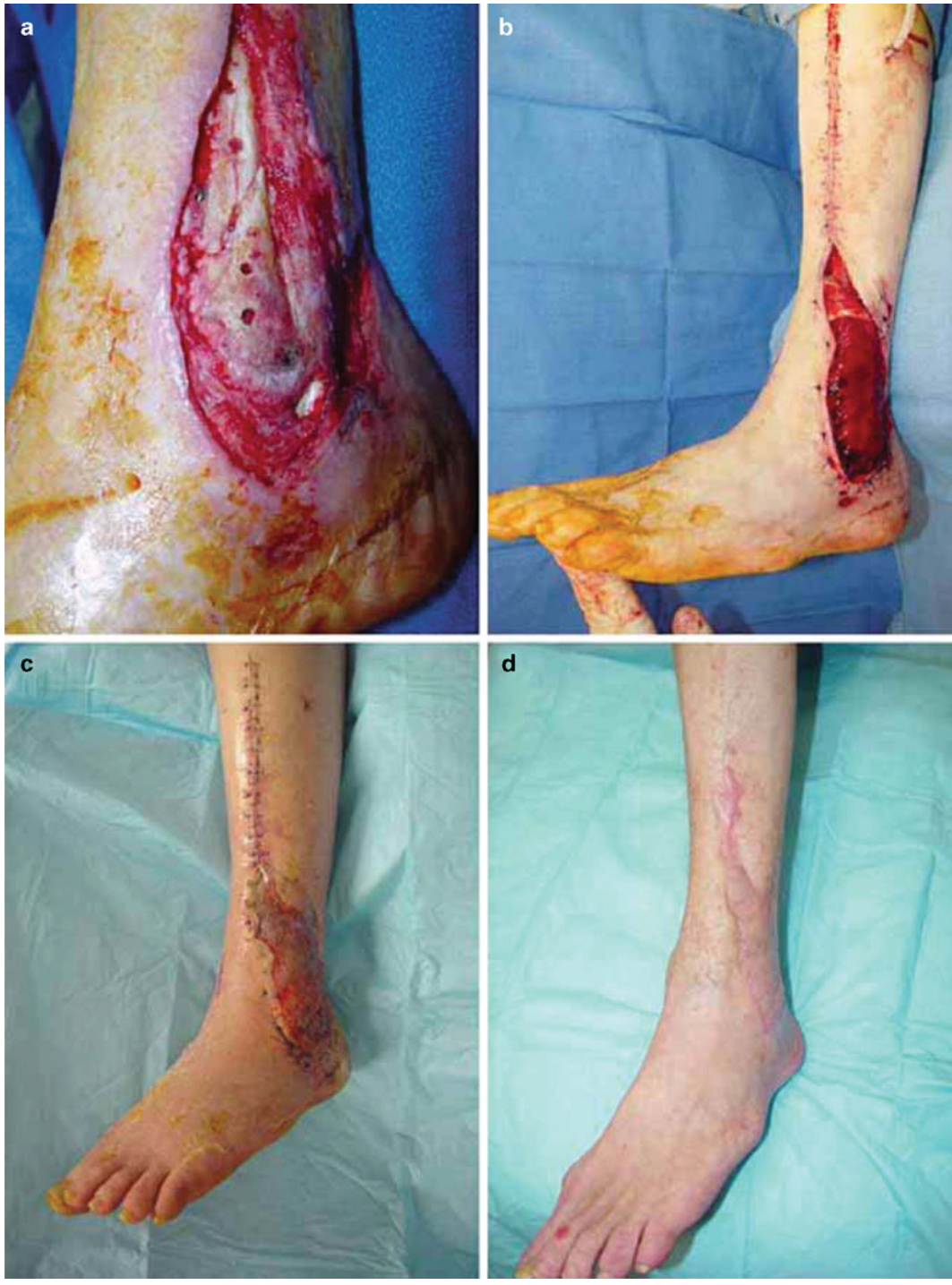

Fig. 21.22 The Extensor Hallucis Longus (EHL) muscle is harvested with the distal third of the anterior tibial artery to cover the lateral distal exposed fibula (**a**, **b**). Dividing the anterior tibial artery can only be done if there is antegrade flow to provide blood supply to the proximal anterior compartment muscles and retrograde flow to feed the flap. The muscle is skin grafted (**c**). The EHL tendon distal to the harvest is tenodesed to the Extensor Digitorum Longus (EDL) so that the hallux maintains its position during gait (**d**)

Lower Leg and Ankle Flaps: Fasciocutanous Flaps

Fasciocutaneous flaps are useful for reconstruction around the foot and ankle although the donor site usually has to be skin grafted [73]. The Retrograde Peroneal flap (*retrograde peroneal artery*) [74] is useful for ankle, heel, and proximal dorsal foot defects. Its blood flow is retrograde and depends on an intact distal peroneal arterial–arterial anastomosis with either or both the anterior tibial artery and/or posterior tibial artery. The dissection is tedious and it does sacrifice one of the three major arteries of the leg. A similar retrograde anterior tibial artery flap [75] fasciocutaneous flap (*retrograde anterior tibial artery*) has been described for coverage in young patients with traumatic wounds over the same areas. Because the anterior compartment is the only compartment of the leg whose muscle depend solely on the anterior tibial artery, only the lower half of the artery can be safely harvested as a vascular leash. The retrograde sural nerve flap [76] (*retrograde sural artery*) is a versatile neurofasciocutaneous flap that is useful for ankle and heel defects (Fig. 21.23). The sural artery travels with the sural nerve and receives retrograde flow from a peroneal perforator 5 cm above the lateral malleolus. The artery first courses above the fascia and then goes deep to the fascia at mid-calf while the accompanying lesser saphenous vein remains above the fascia. The venous congestion often seen with this flap can be minimized if the pedicle is harvested with 3 cm of tissue on either side of the pedicle and with the overlying skin intact [77]. Problems with the venous drainage can be further helped by delaying the flap 4–10 days earlier by first tying off the proximal lesser saphenous vein and sural artery. The inset of the flap is critical to avoid kinking of the pedicle. Ingenious splinting often has to be designed to keep pressure off of the pedicle while the flap heals (the use of the Ilizarov external frame can be very useful in this regard). The major donor deficit of the flap is the loss of sensibility along the lateral aspect of the foot and a skin grafted depression at the posterior calf donor site that may pose a problem if the patient later has to undergo a below knee amputation. The supramalleolar flap (*superior cutaneous branch of the anterior perforating branch of the peroneal artery*) can be used for lateral malleolar and heel defects as well as for dorsal foot defects (Fig. 21.24) [78]. It can be either harvested with the overlying skin or as a fascial layer that can then be skin grafted. When harvested as a fascial layer only, the donor site can be closed primarily.

Small fasciocutaneous flaps based on individual perforators can also be designed over the row of perforators originating from the posterior tibial artery medially and the peroneal artery laterally [79]. Although the reach and size of the flap is limited, it can be expanded by applying the delay principle. These local flaps have proven to be extremely useful in the closure of soft tissue defects around the ankle in patients in an Ilizarov frame because accessibility to the normal flaps or recipient vessels is always a problem (Fig. 21.25).

Foot Flaps: Muscle Flaps

The muscle flaps in the foot have a type 2 vascular pattern with a proximal dominant pedicle, and several distal minor pedicles are useful to cover relatively small local defects [80, 81]. The Abductor Digiti Minimi muscle (*lateral plantar artery*) is very useful for coverage of small mid and posterior lateral defects of the sole of the foot and lateral distal ankle (Fig. 21.26). Its dominant pedicle is just distal and medial to its origin off of the calcaneus and it has a thin distal muscular bulk [82]. The abductor hallucis brevis muscle (*medial plantar artery*) is larger and can be used to cover medial defects of the mid and hindfoot as well as the medial distal ankle (see Fig. 21.25). Its dominant pedicle is at the take-off of the medial plantar artery and its relatively thin distal muscular bulk can be difficult to dissect off the Flexor Hallucis Brevis muscle. The Extensor Digitorum Brevis m. (*lateral tarsal artery*) has disappointingly little bulk but can be used for local defects over the sinus tarsi or lateral calcaneus [83]. The muscle can either be rotated in a limited fashion (Fig. 21.27) on its dominant pedicle, the lateral tarsal artery, or in a wider arc if harvested with the entire dorsalis pedis artery.

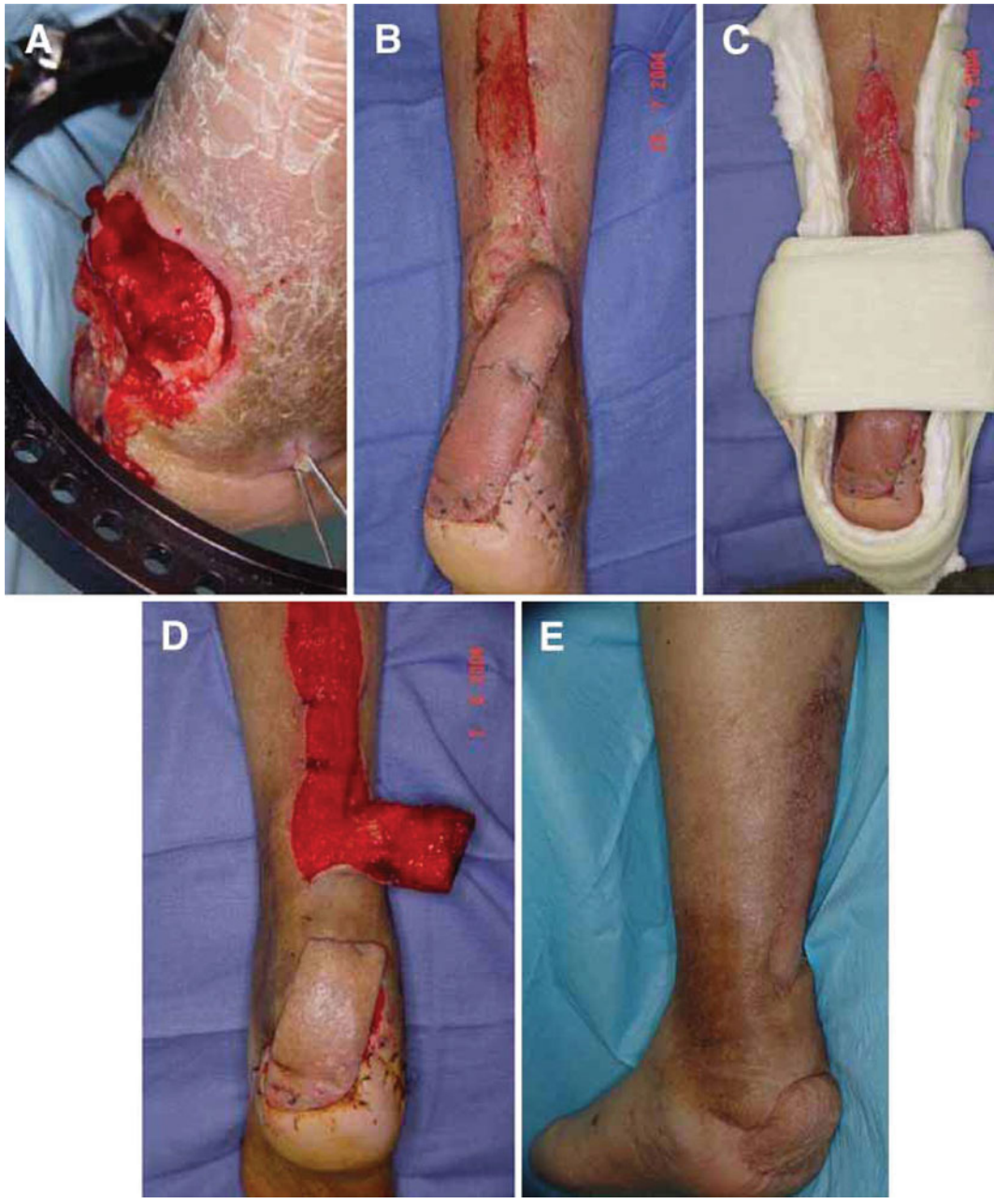

Fig. 21.23 The retrograde sural nerve flap is a versatile neuro-fasciocutaneous flap that is useful for ankle and heel defects. The patient has a heel ulcer with osteomyelitis of the calcaneus (**a**). A sural artery flap is dissected out and inset over the defect (**b**). A cast is designed to offload the heel (**c**). Alternatively an Ilizarov can be applied to offload the heel during healing. After 2 weeks, the pedicle is cut because the flap has developed its own blood supply and the donor defect is skin grafted (**d**). The flap goes on to heal (**e**)

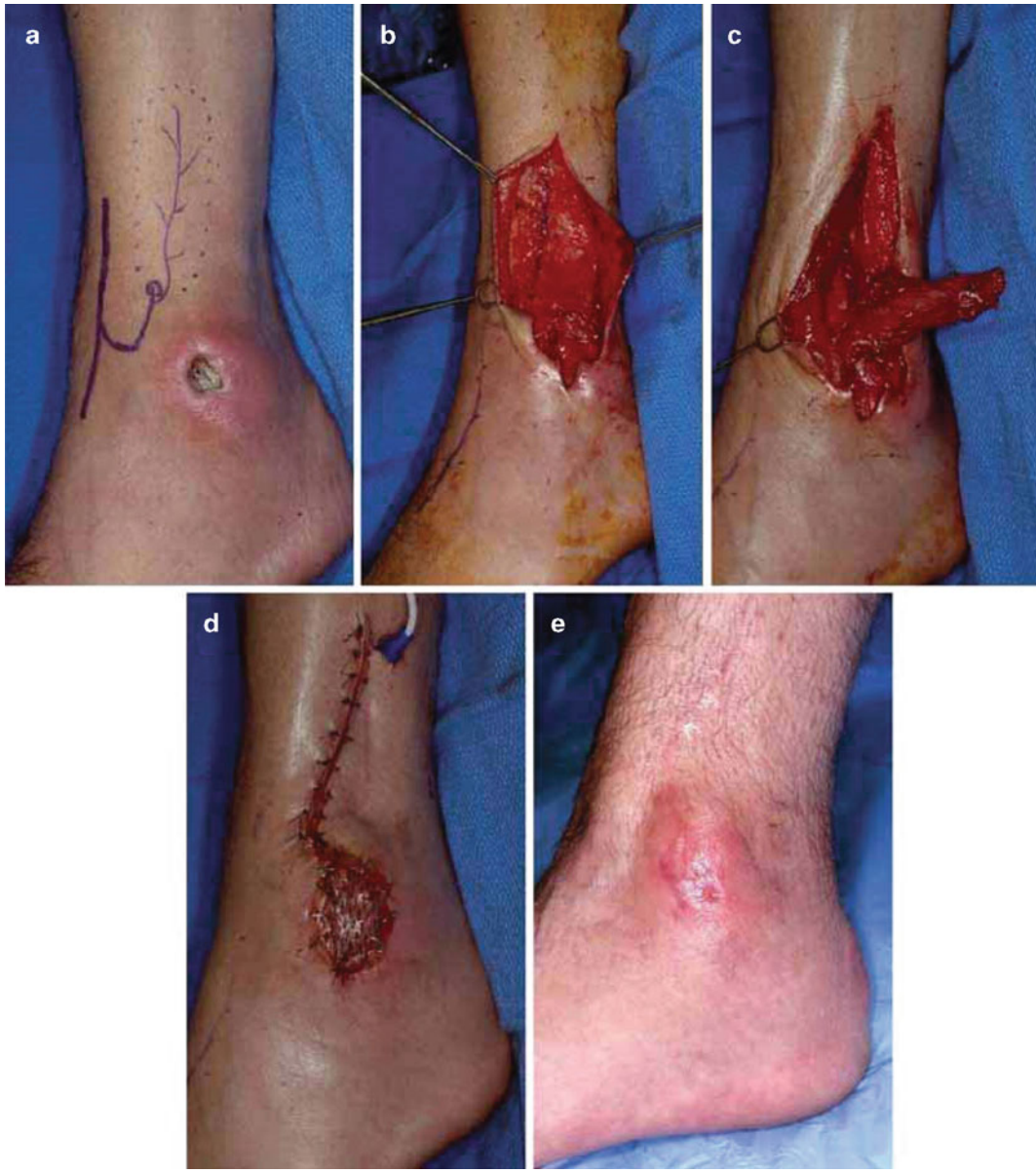

Fig. 21.24 The supra-malleolar flap based on the superior cutaneous branch of the anterior perforating branch of the peroneal artery can be used for lateral malleolar (**a**) as well as for dorsal foot defects. When harvested as fasciocutaneous flap (**b**, **c**), it is then skin grafted (**d**). Because of the new blood supply, the ulcer heals without problems (**e**)

The Flexor Digitorum Brevis m. (*type 2*, *lateral plantar artery*) can be used to cover plantar heel defects [84]. Because the muscle bulk is small, it works best if it is used to fill a defect that can be covered with plantar tissue (Fig. 21.28).

Foot Flaps: Fasciocutaneous Flaps

The most versatile fasciocutaneous flap of the foot is the Medial Plantar flap that is the ideal tissue for the coverage of plantar defects [85–87]. It can also reach medial ankle defects. It can be

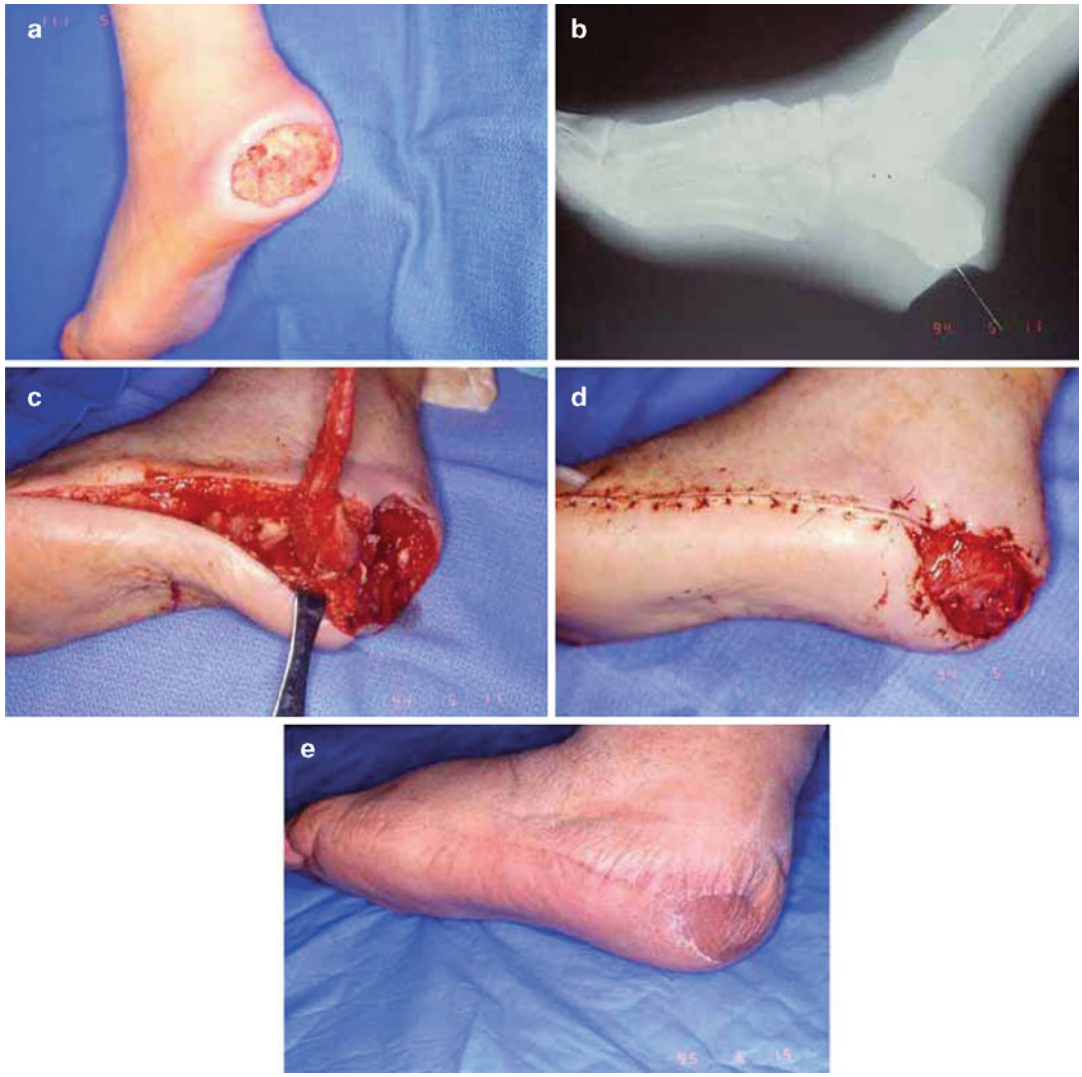

Fig. 21.25 The Abductor Digiti Minimi muscle (*lateral plantar artery*) is very useful for coverage of small mid and posterior lateral defects of the sole of the foot and lateral calcaneal osteomyelitis. The dominant pedicle lies very close to its origin and provides sufficient blood supply so that the minor more distal pedicles can be safely ligated

harvested to a size as large as 6 × 10 cm, has sensibility, and has a wide arc of rotation if it is taken with the proximal part of the medial plantar artery. It can be harvested on the superficial medial plantar artery (*cutaneous branch of the medial plantar artery*) or on the deep medial plantar artery (*deep branch of the medial plantar artery*). It is preferable to harvest the flap with the superficial branch if the artery can be dopplered because it will minimally disrupt the existing foot vascular blood supply (Fig. 21.27). However, if it is to be harvested with retrograde flow, the flap should be harvested with the deep branch of the medial plantar artery. The Lateral Calcaneal flap (*calcaneal branch of the peroneal artery*) is useful for posterior calcaneal and distal Achilles defects (Fig. 21.29) [88]. Its length can be increased by harvesting it as an "L" shape posterior to and below the lateral malleolus [89]. It is harvested with the lesser saphenous vein and

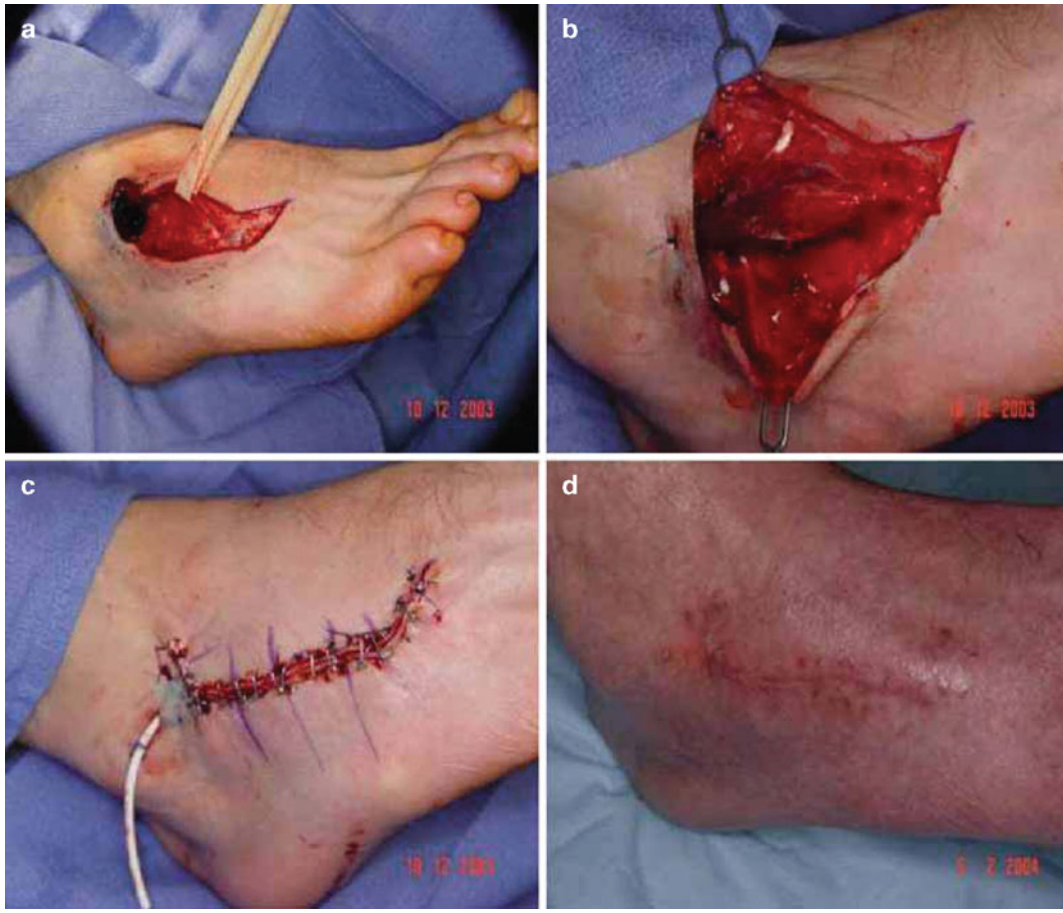

Fig. 21.26 The Extensor Digitorum Brevis m. (*lateral tarsal artery*) has disappointingly little bulk but can be used for local defects over the sinus tarsi or lateral calcaneus. The muscle can either be rotated in a limited fashion on its dominant pedicle, the lateral tarsal artery, or in a wider arc if harvested with the distal anterior tibial artery (antegrade flow) or the proximal dorsalis pedis artery (retrograde flow)

sural nerve. Because the calcaneal branch of the peroneal artery lies directly on top of periosteum, there is a great danger of damaging or cutting it during harvest. The Dorsalis Pedis flap (*dorsalis pedis and its continuation, the first dorsal metatarsal artery*) can be either proximally or distally based for coverage of ankle and dorsal foot defects [90]. A flap wider than 4 cm usually requires skin grafting on top of extensor tendon paratenon which leaves the dorsum of the foot with less than ideal coverage. The loss of the dorsalis pedis can pose problems unless the collateral circulation is intact. Because the donor site is vulnerable both from a vascular and tissue breakdown perspective, this flap is now rarely used. The filet of toe flap (*digital artery*) is useful for small forefoot Web space ulcers and distal forefoot problems although the reach of the flap is always *less* than expected [91]. The technique involves removal of the nail bed, phalangeal bones, extensor tendons, flexor tendons, and volar plates while leaving the two digital arteries intact. A variation of this is the very elegant Toe Island flap where a part of the toe pulp is raised directly over the ipsilateral digital neurovascular bundle [92, 93]. The flap is then elevated with its long vascular leash to cover a distal defect. The vascular leash is buried under the intervening tissue.

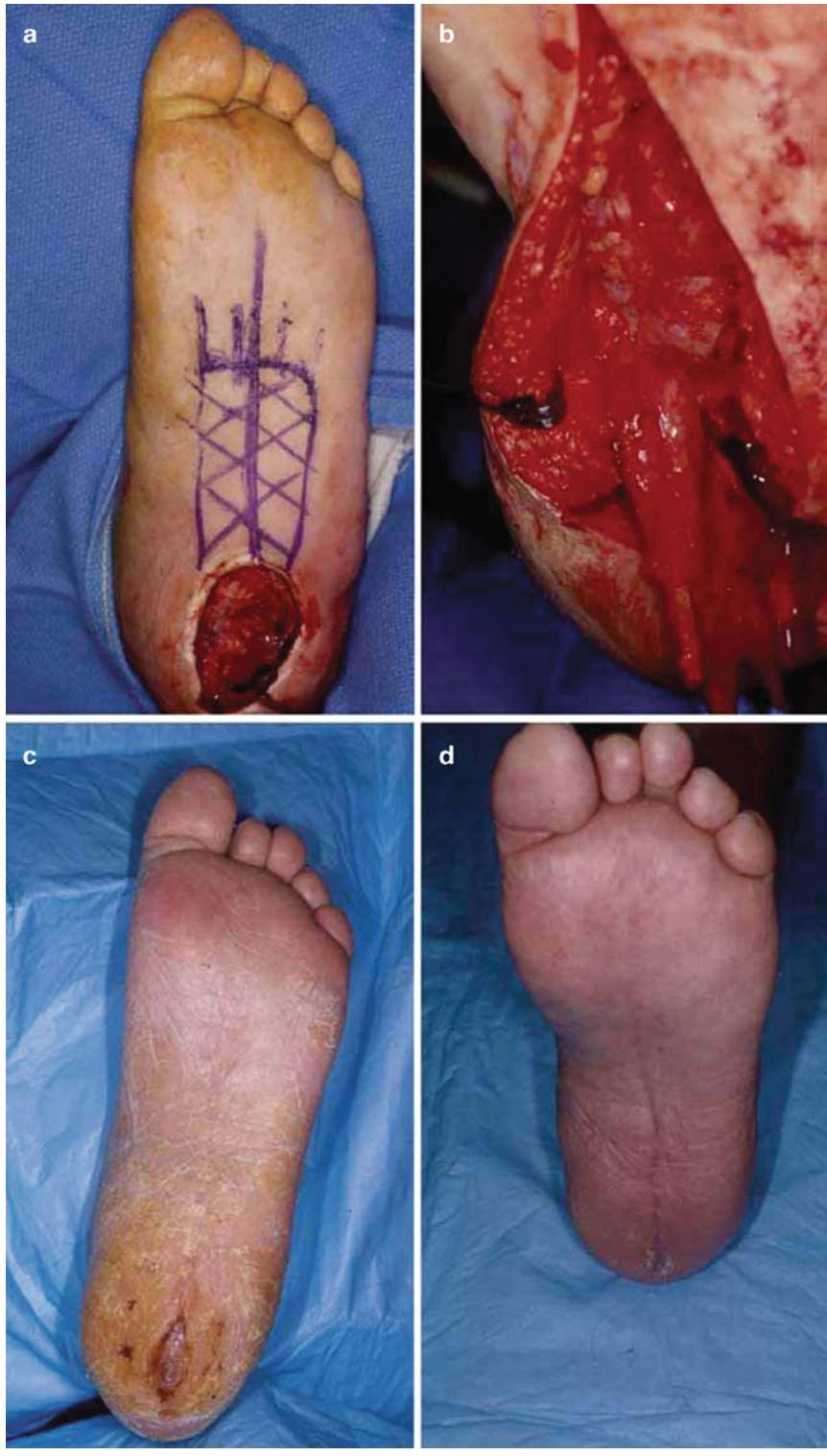

Fig. 21.27 The Flexor Digitorum Brevis m. (*type 2*, *lateral plantar artery*) can be used to cover plantar heel defects. Because the muscle bulk is small, it works best if it is used to fill a defect that can be covered with plantar tissue. Simply skin grafting the muscle often leads to breakdown because of the lack of bulky soft tissue that plantar tissue provides

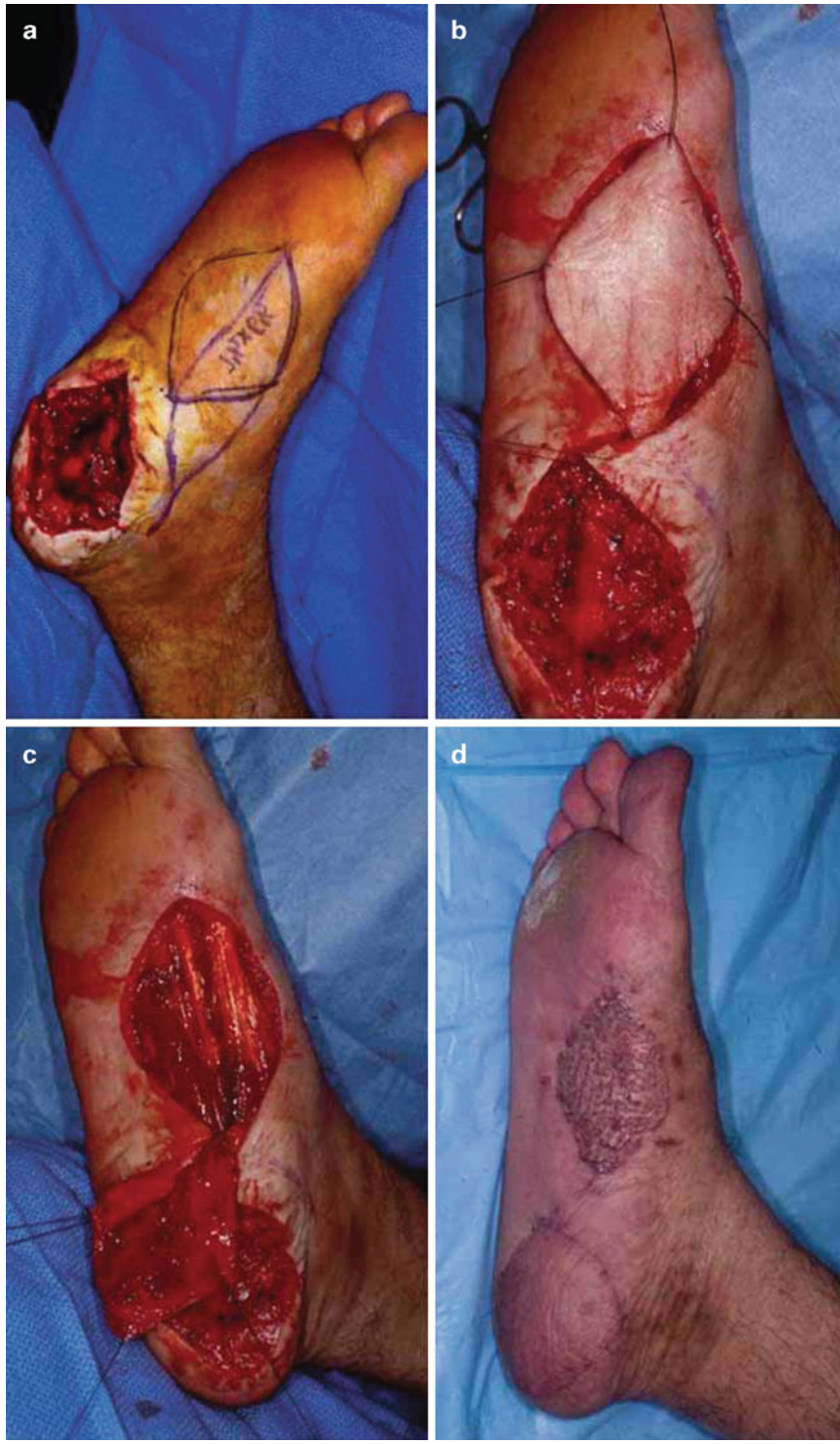

Fig. 21.28 The most versatile fasciocutaneous flap of the foot is the Medial Plantar flap that is the ideal tissue for the coverage of plantar defects. It can be harvested on the superficial medial plantar artery (*cutaneous branch of the medial plantar artery*) or on the deep medial plantar artery (*deep branch of the medial plantar artery*). The flap below is based on the deep medial plantar artery

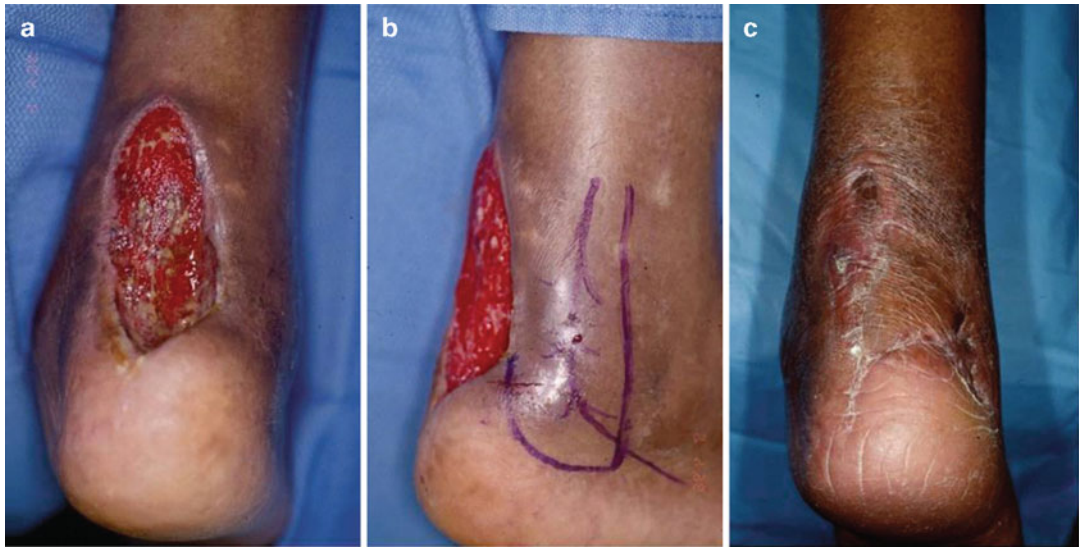

Fig. 21.29 The Lateral Calcaneal flap (*calcaneal branch of the peroneal artery*) is useful for posterior calcaneal and distal Achilles defects. It is harvested with the lesser saphenous vein and sural nerve. Because the calcaneal branch of the peroneal artery lies directly on top of periosteum, there is a great danger of damaging or cutting it during harvest

Complications Associated with Pedicled Flaps

Hematoma creates pressure on the flap which can limit venous return and eventually can lead to flap necrosis. The presence of free blood in the deep space is also cause for concern because the red blood cells themselves release superoxide radicals [94] that can contribute to flap necrosis. Hematoma can be prevented by meticulous hemostasis, topical agents, and closed suction drainage. Postoperatively, it is important to visualize the flap and an occlusive transparent dressing facilitates this. If there is any suspicion of existing hematoma, then the wound should be explored and the hematoma evacuated. If the flap was closed with interrupted sutures, removal of one or two stitches allows for evacuation of the hematoma without risking the disruption of the whole repair. It is important to flush the space with normal saline to get rid of any remaining hemolyzed blood. If the hematoma cannot be removed in this way, the patient should be returned to the O.R. for formal evacuation. External pressure by applying a bandage so that it does not allow for normal postoperative soft tissue swelling or too tightly can also impede blood flow.

Infection can damage or destroy a flap by increasing the metabolic demand of the flap so that it outstrips existing blood supply and occluding the capillary bed which short-circuits vascular flow and leads to arterial occlusion. It is therefore important not to plan a reconstruction before all signs of infection are gone. This means that the skin edges are soft with no surrounding induration or erythema, that the pain has diminished, that there is minimal drainage, and that there are signs of healing (granulation and neoepithelialization). This may require serial debridements that may take up to 1 month before the wound is ready.

Microsurgical Free Flap

Large hindfoot wounds (>6 cm), defects in patients devoid of the posterior tibial vessels (from either trauma or disease), or patients who have been revascularized to the distal anterior

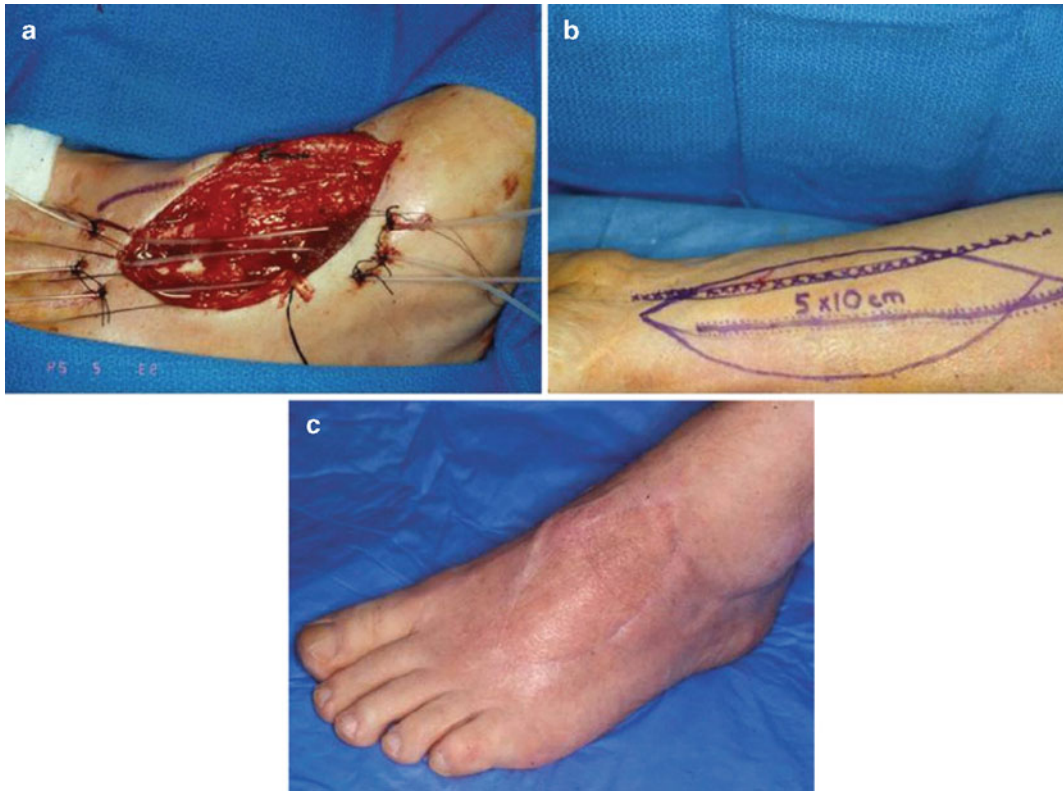

Fig. 21.30 This dorsal foot defect occurred after resection of a sarcoma. The radial forearm flap was harvested with tendon and nerve. The reconstruction included tenodesing the proximal and distal toe extensors with a vascularized palmaris tendon to restore the dorsifleion of the toes. Sensory innervation was obtained by anastamosing the lateral antecubital nerve to the superficial peroneal nerve

tibial/dorsalis pedis artery via bypass grafts should be considered for reconstruction that utilize microsurgical techniques. With the exception of the sural artery flap, all of the regional flaps described for hindfoot repair require antegrade blood flow in the posterior tibial artery and its branches (medial and lateral plantar arteries).

Large dorsal foot wounds with bone and/or tendon exposure are best reconstructed with "thin" free flaps. Thin skin flaps or fascial flaps surfaced with a skin graft will provide durable, thin cover that is esthetically pleasing and permits normal shoe wear. Some skin flaps may also be sensate if harvested with the sensory nerve that supports the flap. They can include vascularized tendon or bone for specific reconstructive tasks. Flaps that have proven to be very successful include the radial forearm flap, the lateral arm flap, the parascapular or dorsal thoracic fascia flap, and the anterolateral thigh (ALT) flap.

The parascapular flap based on the circumflex scapular artery is an excellent choice for large defects [95, 96]. It is insensate, and often needs to be thinned at a later date because of its bulkiness. Colen et al. have described an adaptation of the flap where only fascia with a thin layer of overlying fat is harvested [97]. It is then skin grafted to yield an ultimately far thinner flap.

The lateral arm flap based on the posterior radial recurrent vascular pedicle was first described by Katseros et al. [98]. It is a sensory flap (lower lateral cutaneous nerve of the arm) with a relatively long vascular pedicle (up to 14 cm). Including the skin overlying the elbow can extend the flap size.

The radial forearm flap (Fig. 21.30) is an excellent option for dorsal foot wounds [99, 100]. The advantage of the radial forearm flap is that it is thin, pliable, and can be harvested with a sensory nerve (the lateral antebrachial cutaneous nerve). The palmaris longus tendon can also be used to reconstruct missing extensor tendons on the dorsum of the foot if necessary. The radial forearm flap is also very useful around the malleoli. The radial artery with the venous comitantes provides an excellent vascular pedicle up to 14 cm in length. The flap, if inset properly at the time of flap transfer, rarely needs tailoring. The donor site is skin grafted with or without Integra, and apart from the obvious resulting color disparity, is very manageable.

The ALT flap is a septocutaneous flap based upon perforators originating from the descending branch of the lateral circumflex femoral system [101]. Originally described by Song [102] and popularized by Koshima [103, 104], the anterior lateral thigh flap is well accepted and can supply a large amount of subcutaneous fat and skin on a safe and reliable pedicle with no functional donor site morbidity. The flap may be raised both sensate with the lateral femoral cutaneous nerve and as a flow through flap [105]. Thinning of the flap is well tolerated even to the level of the subdermal plexus for tailoring to a particular defect [106]. The anatomy and dissection of ALT flaps has been well established for both head and neck and lower extremity defects [107].

Pedicled instep flaps are frequently used in weight-bearing plantar reconstruction, but may not be available after severe foot injuries. Gaining popularity is the contralateral sensate free instep flap for reconstruction of a defect with "like tissue" [108]. This flap yields both excellent functional and esthetic long-term results.

Muscle flaps are preferred over exposed bone on the plantar aspects of the foot. Muscle flaps show better resistance against infection when compared with skin flaps. This holds especially true in patients with osteomyelitis. As in other locations, the use of muscle to obliterate dead space and aid in delivering both neutrophils and parenteral antibiotics to regions of chronic osteomyelitis is particularly important [109, 110]. The most frequently harvested muscles include the rectus abdominus muscle, gracilis muscle, and serratus anterior muscle. A word of caution with respect to the use of the latissimus dorsi flap: while this flap is an attractive option in many other parts of the body, the functional loss of the latissimus dorsi must be taken into account in lower extremity reconstructions where many of these patients will be crutch or wheelchair dependent for a prolonged amount of time.

There is still some debate whether muscle plus skin graft versus fasciocutaneous flaps on the plantar surface of the foot holds up better under the stress of ambulation. Muscle flap and a skin graft are currently favored on the plantar aspect of the foot [111, 112]. Muscle flaps provide a better blood supply to the recipient site, making them the better choice for previously infected wounds [113]. If the fasciocutaneous flaps are innervated they could potentially be more effective on the sole of the foot in nonneuropathic patients [114]. Fasciocutaneous flaps are ideal for providing skin coverage while preserving underlying tendon motion. The rectus abdominus muscle flap [115] is very useful because it is easy to harvest, has an excellent pedicle, and is a thin broad muscle. If the muscle is stretched over the recipient site, it may be made even thinner. The donor site morbidity is minimal. The gracilis muscle [116] (Fig. 21.31) is also an excellent choice for foot and ankle reconstruction [117]. It should be harvested from the ipsilateral leg. This limits all incisions to the same extremity. The pedicle is somewhat smaller and shorter than that of the rectus abdominus muscle.

Free flap muscle transfers to the foot tend to swell, which makes it more difficult to fit the foot into a shoe. To minimize this swelling, several technical maneuvers may be helpful. First, the outflow should be optimized by performing two vein anastomoses. To minimize the profile of the flap, it should be inset under tension so that it lies flat and at the same height as that of the surrounding tissue. After the flap has survived and the skin graft has healed, compression therapy helps in improving the overall contour. Stockings with

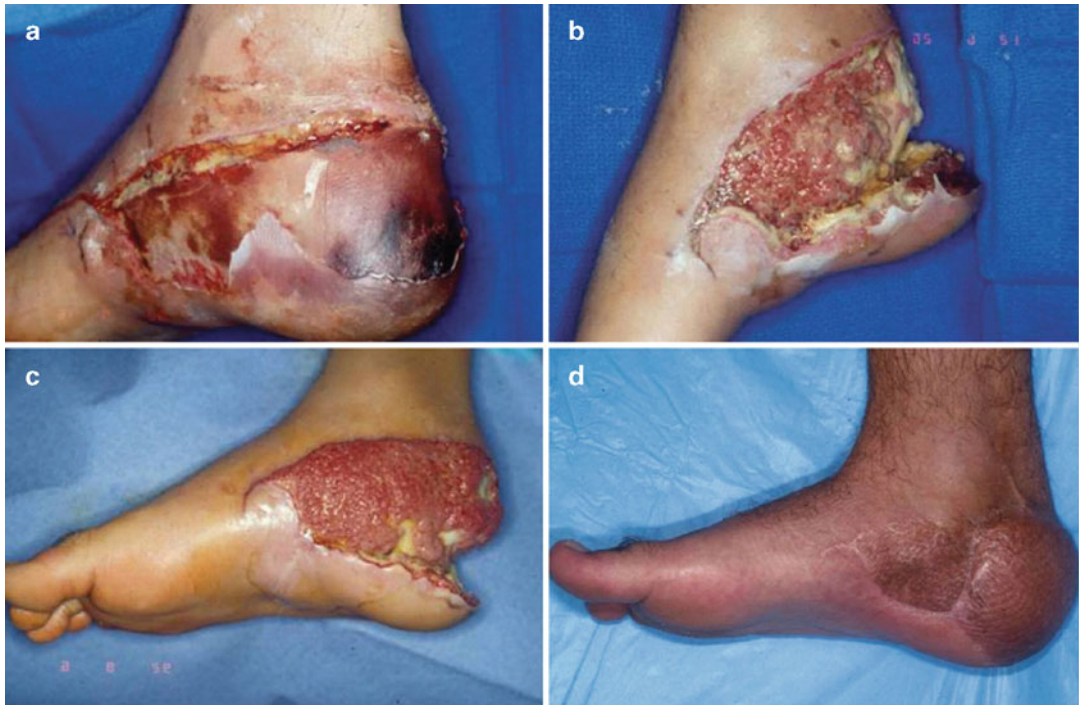

Fig. 21.31 This diabetic patient had an avulsion injury over the right heel (**a**). The wound was serially debrided (**b**) until a healthy base wound healing base was achieved (**c**). A serratus muscle flap with skin graft was used to over the heel. This is the appearance of the foot 5 years later (**d**)

at least 30 mmHg should be worn by the patient. If that is insufficient, the muscle may need debulking. With many of the described flaps, a neurorrhapy may be performed to improve reinervation. Outcomes and overall benefit of this added procedure remain controversial. Some studies report no difference in flap survival or ulceration rates between innervated and noninnervated flaps. Regardless of age or attempted nerve coaptation, patients with neuropathies or heavy scarring due to chronic wounds may not show improvements in flap reinnervation when compared to surrounding tissue [118].

May and others reviewed their experience with patients who underwent free muscle transplantation and split-thickness skin grafting to the weight-bearing portions of the foot and concluded that cutaneous sensibility did not appear to be necessary to maintain a functional and well-healed extremity [119]. In a similar report, Stevenson and Mathes [120] also noted successful coverage of a weight-bearing plantar defect after use of microvascular transplantation of muscle with skin graft coverage. Levin and colleagues reviewed the Duke experience with free tissue transfer to the lower extremity and presented a subunit principle to foot and ankle reconstruction [121]. The authors noted that bulky or ill-conceived flap designs may interfere with proper shoe fitting and prevent efficient ambulation. For plantar reconstructions, flaps that developed late ulceration were more likely to include a cutaneous paddle, with the breakdown usually occurring at the flap/glaborous skin junction. Levin advocates cutting the edge of the flap and the glaborous skin obliquely to maximize the interface surface area as this may decrease the effect of shearing forces. True to all free flap reconstructions, importance should be placed on meticulous flap inset, removal of underlying bony prominences, patient education, and frequent follow-up.

Reconstructive Options by Location of Defect

Forefoot Coverage

Toe ulcer or gangrene is best treated with a limited amputation that uses all remaining viable tissue so that the amputated toe is as long as possible when closed. The surgeon should attempt to at least preserve a sufficient portion of the proximal phalanx to act as a spacer preventing the adjacent toes from drifting into the empty space. If the hallux is involved, attempts should be made to preserve as much length as possible because of its critical role in ambulation [122]. A toe island flap from the second toe is an excellent way to fill a defect on the hallux without having to resort to shortening it.

Ulcers under the metatarsal head(s) occur because biomechanical abnormalities place excessive or extended pressure on the plantar forefoot during the gait cycle. Although hammer toes are contributing factors and should be corrected, the principal cause of the abnormal biomechanical forces is usually a tight Achilles tendon that prevents ankle dorsiflexion beyond the neutral position. A percutaneous release of the Achilles tendon is performed if both portions of the Achilles tendon are tight while a Gastrocnemius recession is performed if only the Gastrocnemius portion of the Achilles tendon is tight. With the release of the Achilles tendon, forefoot pressures drops dramatically and the ulcer(s), if it does not involve bone, should heal by secondary intention in less than 6 weeks [123, 124]. This decrease in push-off strength persists and prevents recurrent ulceration by over 50% over the next 25 months [9, 10].

The complications associated with the Gastrocnemius recession are far less than those associated with the percutaneous Achilles tendon release. The primary complication of a Gastrocnemius recession is a hematoma from tears in the underlying soleus muscle. On the other hand, an overaggressive percutaneous release of the Achilles tendon leads to over lengthening and subsequent calcaneal gait and eventual plantar heel ulcers (13–14%) that are extremely difficult to heal. Healing may require retightening the Achilles tendon or ankle fusion in addition to treating the ulcer.

For patients with normal ankle dorsiflexion who have a stage 1–3 plantar ulcer under metatarsal head due to a plantarly prominent metatarsal head, the affected metatarsal head can be elevated with pre-planned osteotomies and internal fixation. The metatarsal head is thus shifted 2–3 mm superiorly. Upward movement with its attendant pressure relief is usually sufficient for the underlying ulcer to heal by secondary intention. There should not be any transfer lesions to the other metatarsal heads because the anatomic metatarsal head parabola will be preserved. However, if the metatarsal head has osteomyelitis, it should be shaved or resected. The ulcer should heal by secondary intention if all weight is kept off the forefoot while it heals. The small deep forefoot ulcers without an obvious bony prominence can also be closed with a local flap: a filleted toe flap, a toe island flap, a bilobed flap, a rotation flap, a Limberg flap, or a V–Y flap. For larger ulcers where the metatarsal head has been resected, consideration should be given to ray amputation. Resecting the more independent first or fifth metatarsal causes less biomechanical disruption than the second, third, or fourth metatarsal because the middle metatarsals operate as a cohesive central unit.

All efforts should be made to preserve as much of the metatarsals as possible if more than one is exposed because they are so important to normal ambulation. Local tissue is often insufficient to do this in the forefoot and therefore a microsurgical free flap should be considered. If ulcers are present under several metatarsal heads or if a transfer lesion from one of the resected metatarsal head to a neighboring metatarsal has occurred, consideration should be given to doing a pan-metatarsal head resection. This is performed with two or three dorsal incisions and great care is taken to preserve the proportional lengths of each metatarsal so that the normal distal metatarsal parabola is preserved. Removing

the metatarsal heads while leaving the flexors and extensors to the toes intact helps prevent the inevitable equino-varus deformity that accompanies loss of the distal extensors.

If more than two toes and the accompanying metatarsals heads have to be resected, then a transmetatarsal amputation [125] should be performed. The normal parabola with the second metatarsal being the longest is preserved. All bone cuts should be made so that the plantar aspect of the cut is shorter than the dorsal one. If the extensor and flexor tendons of the fourth and fifth toe are intact, they should be tenodesed with the ankle in the neutral position. This helps prevent the subsequent equino-varus deformity from the loss of extensor forces that usually leads to breakdown under the distal fifth metatarsal head. If the Achilles tendon is tight, it should be lengthened [126]. As much plantar tissue as possible should be preserved so that the anterior portion of the amputation consists of healthy plantar tissue. When there are existing medial or lateral defects, the plantar flap should be appropriately rotated to cover the entire plantar forefoot. Dog ears should be resected so that the distal end is as normally tapered as possible and easy to fit into a shoe with a simple orthotics and filler.

The most proximal forefoot amputation is the Lisfranc amputation where all the metatarsals are removed [127]. The direction of the blood flow along the dorsalis pedis and lateral plantar arteries should be evaluated. If both have antegrade flow, then the connection between the two can be sacrificed. However, if only one of the two vessels is providing blood flow to the entire foot, the connection has to be preserved. To prevent an equino-varus deformity, one can either address the anterior tibialis tendon or the Achilles tendon. The anterior tibial tendon can be split so that the lateral half is inserted into the cuboid bone. Alternatively, the Achilles tendon has to be lengthened. The Lisfranc amputation can be closed with volar or dorsal flaps if there is sufficient tissue. If there is not adequate tissue for coverage, a free muscle flap with skin graft should be used. Postoperatively, the patient's foot should be placed in slight dorsiflexion until the wound has healed.

Midfoot Coverage

Defects on the medial aspect of the sole are non-weight bearing and are best treated with a skin graft. Ulcers on the medial and lateral plantar midfoot are usually due to Charcot collapse of the midfoot plantar arch. If the underlying shattered bone has healed and is stable (Eichenholtz stage 3), then the excess bone can be shaved via a medial or lateral approach while the ulcer can either be allowed to heal by secondary intention or can be covered with a glabrous skin graft or a local flap. For small defects, useful local flap include the V to Y flap, the rotation flap, the bilobed flap, the rhomboid flap, or the transposition flap. If a muscle flap is needed, a pedicled Abductor Hallucis flap medially or an Abductor Digiti Minimi flap laterally works well. For slightly larger defects, large V–Y flaps, random large medially based rotation flaps, or pedicled medial plantar fasciocutaneous flap can be successful. Larger defects should be filled with free muscle flaps covered by skin grafts. Great care should be taken inset the flap at the same height as the surrounding tissue. If the Charcot midfoot bones are unstable (Eichenholtz stage 1 or 2), then they can be excised with a wedge excision. The bones on either side of the resection are then fused to recreate the normal arch of the foot and held in place with an Ilizarov frame. The shortening of the skeletal midfoot usually leaves enough loose soft tissue to close the wound primarily or with a local flap.

Hindfoot Coverage

Plantar heel defects or ulcers are among the most difficult of all wounds to heal. If they are the result of the patient being in a prolonged decubitus position, they are also usually a reflection of severe vascular disease. A partial calcanectomy may be required to develop enough of a local soft tissue envelope to cover the resulting defect. Although patients can ambulate with a partially resected calcaneus, they will need orthotics and molded shoes. If there is an underlying collapsed bone or bone spur causing a hindfoot defect, the bone should be shaved down. These ulcers are

usually closed with double V–Y flaps or larger medially based rotation flaps. Plantar heel defects can also be closed with pedicled flaps that include the medial plantar fasciocutaneous flap or the Flexor Digiti Minimi muscle flap. Posterior heel defects are better closed with extended lateral calcaneal fasciocutaneous flap or the retrograde sural artery fasciocutaneous flap. If the defect is large, then a muscle-free flap with skin graft should be used. The flap should be carefully tailored so there is no excess tissue and it blends in well with the rest of the heel. Medial or lateral calcaneal defects usually occur after fracture and attempted repair. If this results in osteomyelitis of the calcaneus, the infected bone should be debrided and antibiotic beads should be placed. The defect can usually be covered with the Abductor Hallucis muscle flap medially or the Abductor Digiti Minimi flap laterally. The exposed muscle is then skin grafted. After 6 or more weeks, the beads can be replaced with bone graft. Consideration should be given to applying an Ilizarov frame during the healing phase for heel defect because it protects the soft tissue repair from pressure by suspending the heel and immobilizes the ankle so that sheer forces cannot disrupt the repair.

The two hindfoot amputations are the Chopart and Symes amputations. The Chopart amputation leaves an intact talus and calcaneus while removing the mid and forefoot bones of the foot. To avoid going into equino-varus deformity, a minimum of 2 cm of the Achilles has to be resected so that the connection between the two parts of the Achilles tendon have no chance of healing together. When the amputation has healed, a calcaneal-tibial rod can be used to further stabilize the position of the calcaneus. The Symes amputation should be considered if there is insufficient tissue to primarily close a Chopart amputation and the talus and calcaneus are involved with osteomyelitis. The tibia and fibula are cut just above the ankle mortise and the deboned heel pad swung anteriorly. The heel pad has to be anchored to the anterior portion of the distal tibia to prevent posterior migration. The ultimate goal is a thin, tailored stump that can fit well into a patellar weight bearing prosthesis. A poorly designed Symes amputation is a prosthetist's nightmare and can lead to repeated breakdown of the stump.

Dorsum of the Foot

The defects on the dorsum of the foot are often treated with simple skin grafts. If the tissue covering the extensor tendons is thin or nonexistent, a dermal regeneration template (Integra) should be applied. When the dermis is vascularized, a thin skin autograft is then applied (Fig. 21.32). Local flaps that can be used for small defects include rotation, bilobed, rhomboid, or transposition flaps. Possible pedicled flaps include the Extensor Digitorum Brevis muscle flap, the dorsalis pedis flap, the supra-malleolar flap, and the sural artery flap. The EDB muscle's reach can be increased by cutting the dorsalis pedis artery above or below the lateral tarsal artery, depending on where the defect is and whether there is adequate antegrade and retrograde flow. The reach of the supra-malleolar flap can be increased by cutting the anterior perforating branch of the peroneal artery before it anastomoses with the lateral malleolar artery. For defects at the sinus tarsus, the EDB flap works well. The most appropriate microsurgical free flap is a thin fasciocutaneous flap to minimize bulk. The radial forearm flap is an excellent choice because it is sensate and provides a vascularized tendon (palmaris tendon) to reconstruct lost extensor function. Thin muscle flaps with skin grafts or fascial flaps are effective options as well.

Ankle Defects

Soft tissue around the ankle is sparse and has minimal flexibility. If there is sufficient granulation tissue, a skin graft will work well. To encourage the formation of a healthy wound bed, NPWT ± Integra can be used. The Achilles tendon, if allowed sufficient time to form a granulating bed, will tolerate a skin graft that will hold up well over time. Local flaps do not need to cover the entire defect because only the critical area of the wound such as exposed tendon, bone, or joints needs to be covered while the rest of the wound can be skin grafted. Useful local flaps include rotation, bilobed, or transposition flaps. Local flaps can easily be individually designed off posterior tibial and peroneal arterial

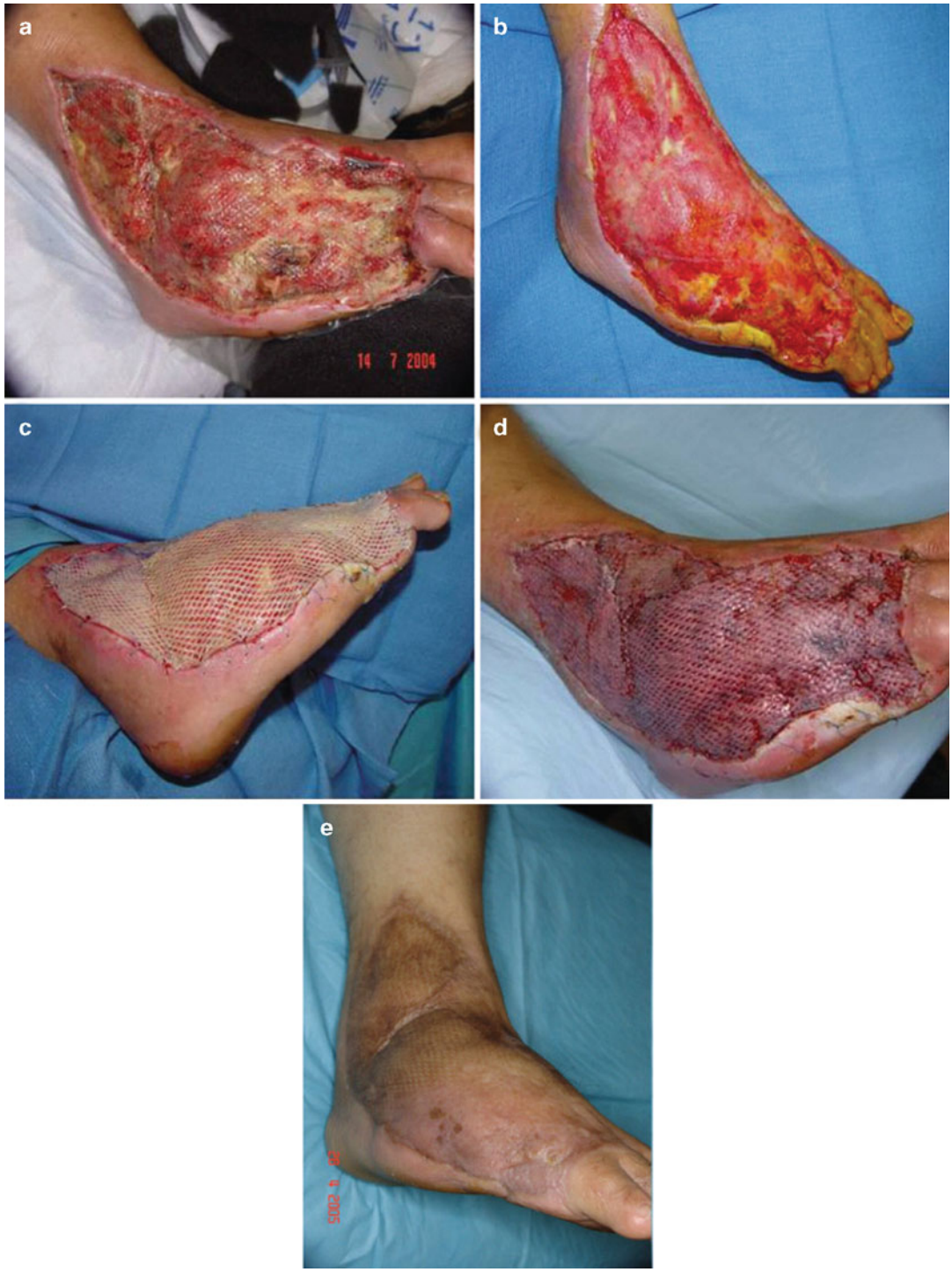

Fig. 21.32 This patient developed necrotizing fasciitis with alpha-hemolytic streptococcus that destroyed the entire dorsum of the foot (**a**). After multiple debridements, the wound was covered with neodermis and NPWT. Neodermis (**b**) was then covered with a skin graft (**c**) and the wound went on to heal without incident (**d**, **e**)

perforators. Pedicled flaps include the supramalleolar flap, the dorsalis pedis flap, the retrograde sural artery flap, the medial plantar flap, Abductor Hallucis muscle flap, the Abductor Digiti Minimi muscle flap, and the Extensor Digitorum Brevis muscle flap. Free flaps can either be fasciocutaneous or muscle with skin graft but they should be kept thin. In order to ensure good healing, the ankle should be temporarily immobilized with an external fixator.

Summary

Treating diabetic foot ulcers and gangrene can only be done effectively by using a team approach which at the minimum includes a wound care team, a vascular surgeon, a foot and ankle surgeon, a plastic surgeon, an infectious disease specialist, an endocrinologist, and a prosthetist. The repair is dictated by how much of the foot remains postdebridement and how the foot can be closed in the most biomechanically stable construct possible. This may involve skeletal manipulation, tendon lengthening, and/or partial foot amputations. Soft tissue reconstruction can be as simple as allowing the wound to heal by secondary intention or as complex as microsurgical free flaps. Wound healing adjuncts such as growth factor, cultured skin, and hyperbaric are helpful adjuncts. Over 90% of the wound can be closed utilizing simple methods from healing by secondary intention to skin grafting. Utilizing this approach should decrease the primary and secondary major amputation rate to below 5%.

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Amputations and Rehabilitation

22

Coleen Napolitano, Ann Zmuda, Ronald A. Sage, Michael Pinzur, and Rodney Stuck

Abstract

An amputation of the lower extremity is erroneously considered as a failure of conservative care or an unpreventable outcome of diabetes. In the diabetic population, a lower extremity amputation is often the result of ischemia or uncontrolled infection. This chapter discusses multiple factors that should be evaluated to optimize the outcome of any amputation. The technique and important intraoperative factors when performing an amputation are discussed. Following an amputation, a rehabilitation process is begun to return the patient back into the community. Discussed are the factors that influence a patient's rehabilitation potential as a community ambulator.

Keywords

Diabetes • Limb salvage • Transmetatarsal amputation • Below-knee amputation • Rehabilitation

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Indications and Basic Principles of Amputation

Amputation of the foot may be indicated when neuropathy, vascular disease, and ulcerative deformity have led to soft tissue necrosis, osteomyelitis, uncontrollable infection, or intractable pain.

Amputations of the lower extremity are often considered either a failure of conservative management or an unpreventable outcome of diabetes.

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The patient sees amputation as the end of productivity and the start of significant disability. Amputation should be viewed as a procedure leading to rehabilitation and return to productivity for the patient disabled by an ulcerated, infected, or intractably painful extremity. The patient needs assurance, and efforts should be made to follow up the procedure with efforts to return him or her to productive community activity. This may involve consultation among the specialties of medicine, podiatry, orthopedics, vascular surgery, physiatrist, and prosthetics. As the patient is rehabilitated and returns to the activities of daily living, the residual limb and the contralateral limb must be protected. Revision amputation and amputation of the contralateral limb remain significant problems, occurring in as many as 20% of amputee cases [1].

The goal of any limb salvage effort is to convert all patients' diabetic feet, from Wagner grades 1–4, back to grade 0 extremities. Those patients with grade 5 feet will require an appropriate higher level of amputation. If salvage is not feasible, then all efforts are made to return the patient with some functional level of activity after amputation. The more proximal the amputation, the higher the energy cost of walking. This problem is most significant in our patients who have multisystem disease and limited cardiopulmonary function. These factors may negatively impact the patients' postoperative independence.

Patients may require several surgical treatments before definitive amputation. Incision and drainage or open amputation is frequently required to stabilize acute infection. The parameters of healing, to be mentioned later, may not apply at that time. The goal of the first stage of a multistaged procedure is simply to eradicate infection and stabilize the patient. If medical review of the patient suggests an inability to tolerate multiple operations, a higher initial level of amputation may be indicated foregoing attempts at distal salvage. However, if salvage is possible and the patient is medically stable, then a systematic approach to limb salvage should be pursued.

Limb Salvage Versus Limb Amputation

Enlightened orthopedic care of the new millennium has changed focus from results to outcomes. Burgess taught us that amputation surgery is the first step in the rehabilitation of a patient with a nonfunctionally reconstructable limb [2]. He taught us to focus on the reentry of the amputees into their normal activities, setting achievable functional goals.

Lower extremity amputation is performed for ischemia, infection, trauma, neoplastic disease, or congenital deformity. Irrespective of the diagnosis, the following questions should be addressed before either undertaking an attempt at limb salvage or performing an amputation.

1. Will limb salvage outperform amputation and prosthetic limb fitting? If all transpires as one could reasonably predict, will the functional independence of the patient following limb salvage/reconstruction be greater or less than amputation and prosthetic limb fitting? This will vary greatly with age, vocational ability, medical health, lifestyle, education, and social status.
2. What is a realistic expectation of functional capacities at the completion of treatment? A realistic appreciation of functional end results should be made with respect to both limb salvage and amputation. Consultation with physical medicine and rehabilitation, social work, and physical therapy can assist in determining reasonable outcome expectations.
3. What is the time and effort commitment required for both the treatment team and the patient? Both the physician and patient must have a reasonable understanding of the duration of the rehabilitation process, the inherent risks involved with revascularization, and the effort required for both.
4. What is the expected financial cost to the patient and resource consumption of the health care system? Direct expenses of diabetic foot ulceration and amputations were estimated to cost the US health care payers $10.9 billion in 2001 and increase to $116 billion in 2007.

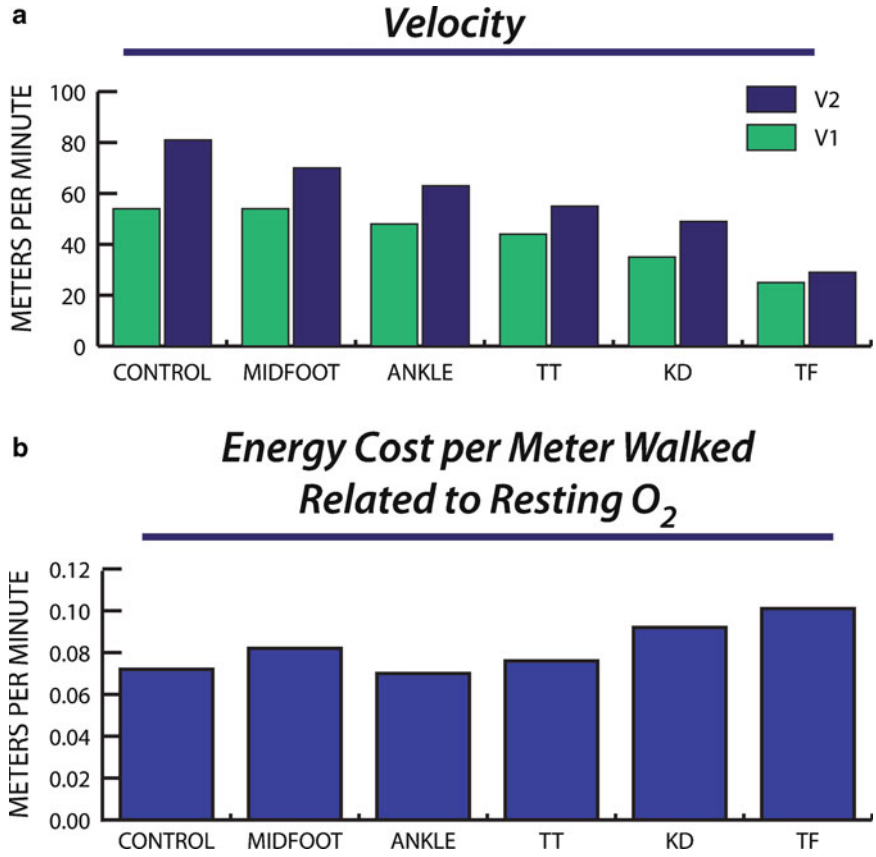

Fig. 22.1 Table of velocity and energy cost. (**a**) Walking velocity compared to surgical amputation level. *V1* is self-selected walking speed. *V2* is maximum walking speed. (**b**) Oxygen consumption per meter walked compared to surgical amputation level. Note that the metabolic cost of walking is increased with more proximal-level amputation

Indirect expense (disability, work loss, and premature mortality) was estimated at $58 billion [3, 4].

Physical and Metabolic Considerations

Metabolic Cost of Amputation

The metabolic cost of walking is increased with proximal-level amputations, being inversely proportional to the length of the residual limb and the number of joints preserved. With more proximal amputation, patients have a decreased self-selected, and maximum, walking speed. Oxygen consumption is increased. From an outcomes perspective, functional independence (functional independence measure score) is directly correlated with amputation levels. Distal-level amputees achieve proportionally higher functional independence measure scores (Fig. 22.1) [5–7].

Cognitive Considerations

It is suggested that many individuals with long-standing diabetes have cognitive and perceptual deficits (Fig. 22.2) [8–12]. There are certain specific cognitive capacities that are necessary for individuals to become successful prosthetic users: memory, attention, concentration, and organization. In order for patients with these deficiencies to become successful prosthetic users, they require either specific, successful education and training or the physical presence of a caregiver that can provide substitute provision of these skills.

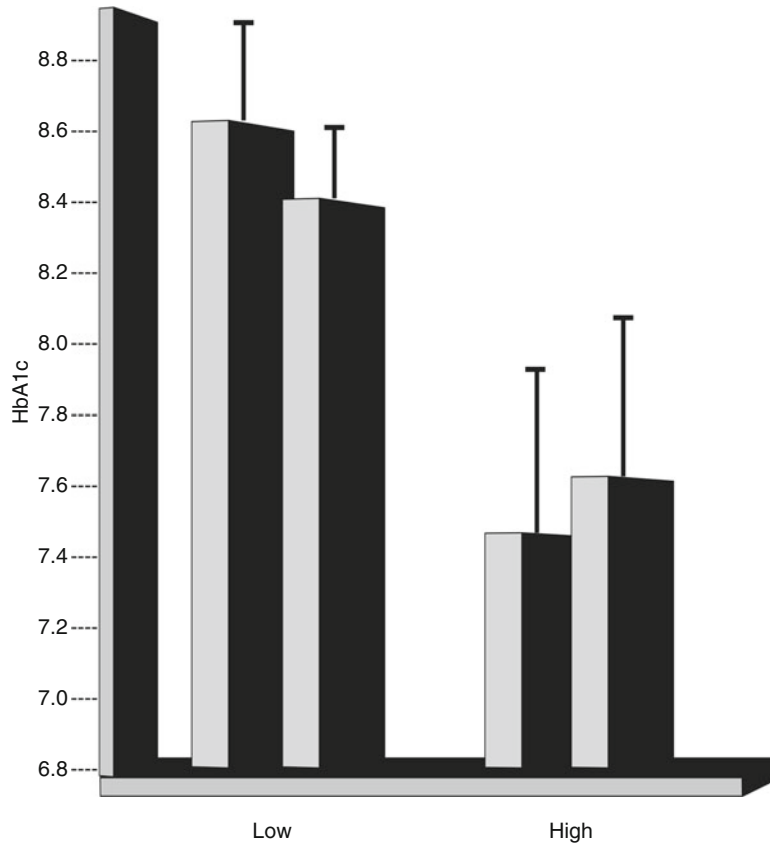

Fig. 22.2 Cognitive table and higher HA1C. Patients with cognitive dysfunction (CIB ≤ 5 or CDT ≤ 13) had a higher A1C, indicating poorer glycemic control compared with patients without cognitive dysfunction ($P < 0.003$ with CIB and $P < 0.05$ with CDT). *Grey bar* CIB; *black bar* CDT

Load Transfer and Weight Bearing

Our feet act as uniquely adapted end organs of weight bearing. Following amputation, the residual limb must assume the tasks of load transfer, adapting to uneven terrain, and propulsion, utilizing tissues that are not biologically engineered for that purpose. The weight-bearing surface of long bones is wider than the corresponding diaphysis. This increased surface area dissipates the force applied during weight bearing over a larger surface area, and the more accommodative articular cartilage and metaphyseal bone allow cushioning and shock absorption during weight bearing.

Direct load transfer, i.e., end bearing, which is achieved in disarticulation amputations at the knee and ankle joint levels, takes advantage of the normal weight-bearing characteristics of the terminal bone of the residual limb. The overlying soft tissue envelope acts to cushion the bone, much as the heel pad and plantar tissues function in the foot.

Indirect load transfer, or total contact weight bearing, is necessary in diaphyseal transtibial and transfemoral amputation levels, where the surface area and stiffness of the terminal residual limb require unloading. The weight-bearing load must be applied to the entire surface area, with the soft tissue envelope acting as a cushion [13] (Fig. 22.3).

Soft Tissue Envelope

The soft tissue envelope acts as the interface between the bone of the residual limb and the

prosthetic socket. It functions both to cushion the underlying bone and dissipate the pressures and forces applied during weight bearing. Ideally, it should be composed of a mobile, nonadherent muscle mass and full-thickness skin. If the soft tissue envelope is adherent to bone, the shear forces will produce skin blistering, ulceration, and tissue breakdown. It should be durable enough to tolerate the direct pressures and pistoning within the prosthetic socket.

Healing Parameters

Vascular Perfusion

Amputation wounds generally heal by collateral flow, so arteriography is rarely a useful diagnostic tool to predict wound healing. Doppler ultrasound has been utilized to assess blood flow in the extremity before amputation. An ankle-brachial index of 0.45 in the patient with diabetes has been considered adequate for healing as long

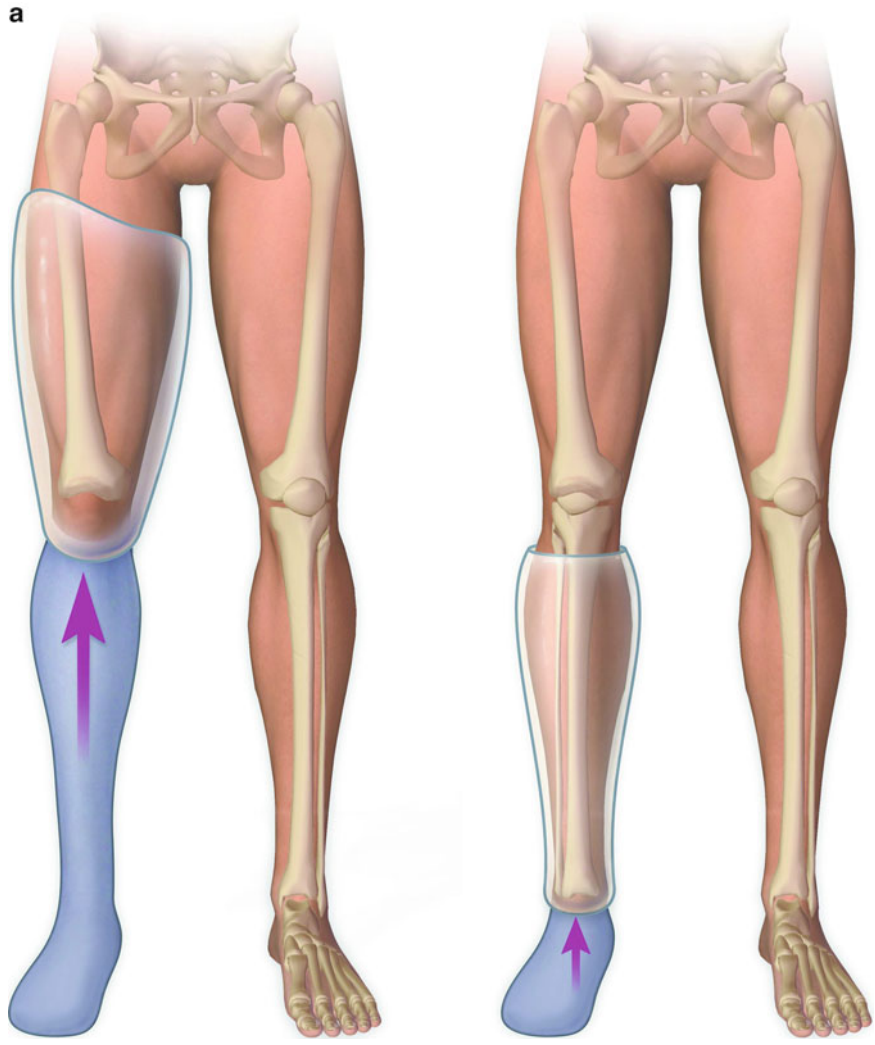

Fig. 22.3 (**a**) Direct load transfer (end bearing) is accomplished in knee disarticulation and Syme's ankle disarticulation amputation levels. (**b**) Indirect load transfer (total contact) is accomplished in transtibial and transfemoral amputation levels

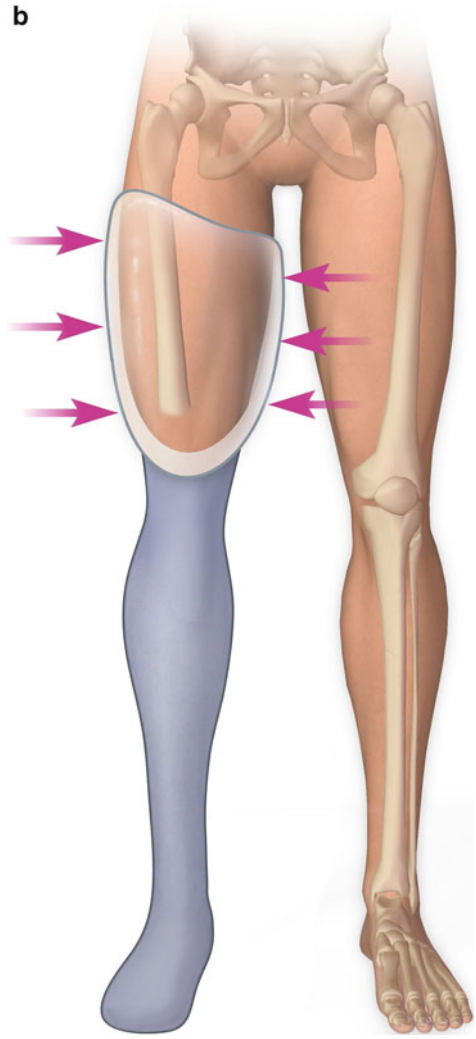

Fig. 22.3 (continued)

as the systolic pressure at the ankle was 70 mmHg or higher. These values are falsely elevated, and nonpredictive, in at least 15% of patients with peripheral vascular disease because of noncompressibility and noncompliance of calcified peripheral arteries [14]. This has prompted the use of varying noninvasive vascular testing modalities, including transcutaneous partial pressure of oxygen ($TcPO_2$), skin perfusion pressure (spp), and toe brachial index (TBI) [15]. Peripheral vascular consultation should be obtained for patients who do not have adequate inflow on these exams. The vascular laboratory can measure toe pressures as an indicator of arterial inflow to the foot. This is owing to the observation that arteries of the hallux do not seem to be calcified, as do the vessels of the leg [16–19]. The accepted threshold toe pressure is 30 mmHg.

Nutrition and Immunocompetence

Preoperative review of nutritional status is obtained by measuring the serum albumin and the total lymphocyte count (TLC). The serum albumin should be at least 3.0 g/dl and the TLC

should be greater than 1,500. The TLC is calculated by multiplying the white blood cell count by the percent of lymphocytes in the differential. When these values are suboptimal, nutritional consultation is helpful before definitive amputation. If possible, surgery in patients with malnutrition or immunodeficiency should be delayed until these issues can adequately be addressed. When infection or gangrene dictates urgent surgery, surgical debridement of infection, or open amputation at the most distal viable level, followed by open wound care, can be accomplished until wound healing potential can be optimized [20–23]. At times such as with severe renal disease, the nutritional values will remain suboptimal and distal salvage attempts may still be pursued, but at known higher risk for failure.

Poor glycemic control has been identified as a risk factor associated with a higher frequency of amputation (Fig. 22.4) [24, 25]. High glucose levels will deactivate macrophages and lymphocytes and may impair wound healing as well as having been associated with other postoperative infections including those of the urinary tract and respiratory system. Ideal management involves maintenance of glucose levels below 200 mg/dl [23]. However, caution must be taken in managing the perioperative patient's glucose with calorie reduction, as this process may lead to significant protein depletion and subsequent wound failure. If the patient's BMI is normal, to provide maintenance and avoid negative nitrogen balance, 25 cal/kg is required.

The combined wound healing parameters of vascular inflow and nutritional status have been studied and shown to significantly affect healing rates for pedal amputations. Attempting to optimize nutrition and perfusion preoperatively, when medically possible, will limit the risk of wound complications and failure.

Perioperative Considerations

Pedal amputations may be performed under local or regional anesthesia. The effectiveness of local anesthetics may be impaired by the presence of infection and may need to be administered proximal to any cellulitis. When amputating above the ankle, spinal or general anesthesia will be necessary. Spinal anesthesia is contraindicated in the patient with sepsis demonstrated by fever over 100°F.

Culture-specific antibiotic therapy should be continued perioperatively. If the focus of infection is completely removed with amputation, then the antibiotics may be discontinued 24 h after surgery. If, however, infection remains a concern, then antibiotics are continued for a soft tissue course of 10–14 days, or 6–8 weeks for bone infection.

Tourniquets may be needed to control bleeding at surgery. The surgeon must ensure that the tourniquet is not placed over a vascular anastomosis site or distal to an area of infection. The patient with severe vascular compromise will not require a tourniquet.

Preoperative Summary

Preoperative planning for distal limb salvage procedures should include the measurement of serum albumin, TLC, and tissue perfusion. With satisfactory values in all three categories, healing rates as high as 90% may be attainable. However, at least 10% of even ideal cases may fail. With impaired nutrition or perfusion, the risk of failure becomes even greater. The patient should be informed of these risks. Efforts should be made to use this information to plan procedures at levels that will limit the patient's exposure to multiple revision attempts. A single surgical session for a transtibial amputation may be preferable to multiple futile attempts at distal salvage in severely compromised or borderline cases.

Ray Amputations

Indications

Single toe amputation or ray resection may be performed for irreversible necrosis of a toe without medial or lateral extension. Deep infection of an ulcer to bone is also an appropriate indication for toe amputation. If uncontrollable infection extends to the metatarsal-phalangeal joint or metatarsal head, ray resection is appropriate. This procedure is also useful for infection or necrosis

Comparison between the major amputation and minor or non-amputation groups in each item

Item	Subgroup	Number (n = 210)	Major Amputation Group	Minor Amputation Group and non-amputation group		x^{2a}	*p* value	
				Minor Amputation Group (n = 65)	Non-amputation group (n = 100)			
Age at the initial examination[b]	A ≥ 65 years	115	32	37	46	0.002	0.964	
	B < 65 years	95	13	28	54			
Sex	A Male	113	37	35	41	2.443		
	B Female	97	8	30	59		0.118	
Duration of Diabetes[b]	A ≥ 18.1 years	96	20	37	39	0.496		
	B < 18.1 years	112	25	28	59		0.481	
HbA1c	A ≥ 8.0%	94	33	36	25	4.409		
	B < 8.0%	116	12	29	75		0.035	*
Neurological Symptoms[c]	A Yes	165	43	58	64	0.283		
	B No	38	0	7	31		0.595	
Retinal Symptoms[c]	A Yes	165	43	58	64	0.139		
	B No	39	1	7	31		0.709	
Renal Symptoms[c]	A Yes (with dialysis)	61	30	18	13	7.875	0.0051	*
	B Yes (without dialysis)	96	11	37	48	0.336	0.562	
	C No	54	4	10	39			
Dialysis[b,c]	A ≥ 6 years	38	22	9	7	3.379	0.053	*
	B < 6 years	22	7	9	6			
ASO (number of cases)[c]	A Yes (with multiple lesions)	71	39	20	12	10.1	0.0015	*
	B Yes (without multiple lesions)	79	5	37	37	1.918	0.1661	
	C No	47	1	8	38			
Ishemic Heart Disease	Yes	64	28	21	15	2.517		
	No	143	17	44	82		0.1126	

[a]Difference in the amputation rates determined by the log-rank test between subgroups fromed by Kaplan-Meier method

[b]Subgroups classified by median value

[c]Some cases are unclear or lacking data

* Significant difference

Fig. 22.4 Glycemic table and higher frequency of amputation

of the toe, requiring more proximal resection to obtain viable wound margins.

Ray resection is an excellent method of decompressing deep fascial infection limited to one compartment of the plantar structures of the foot, be that medial, lateral, or central. In such cases, the wound is always left open to allow continued drainage and resolution of the acute infection. Once stabilized and healing parameters are optimal, the open ray may be followed by a more proximal, definitive procedure [26].

Procedure

First and fifth ray amputations are a wedge resection of the digit and the incision converges along the medial or lateral aspect of the metatarsal, respectively.

Central ray incisions are different from those of the first and fifth rays. Incisions are made on the medial and lateral aspects of the base of the digit and extend proximally on the dorsal and plantar aspects of the foot to converge over the individual metatarsal. If ulceration is present, as frequently occurs plantar to the metatarsal head, the ulcer is resected along with the wedge of soft tissue that includes the affected toe. The initial incisions are carried to bone, and the toe is disarticulated at the metatarsal-phalangeal joint. The periosteum of the metatarsal is reflected as far proximally as necessary down the shaft of the bone in order to assure that the resection is performed at a level of viable, noninfected bone. The bone is usually cut at the proximal diaphysis or diaphyseal-metaphyseal junction. It is rarely necessary to do the extensive dissection required to disarticulate the metatarsal-cuneiform joint.

Once the bone is removed from the wound, the foot is compressed from proximal to distal to assure that there is no remaining ascending purulent drainage. If the flexor or extensor compartments reveal purulence on compression, then they are opened and irrigated to clean out any remaining apparent infection. If the ray resection was performed for metatarsal or plantar space infection, it is left open to allow healing by secondary intention or a delayed primary procedure (Fig. 22.5a, b).

Postoperative Care

The only ray resection that should be closed primarily is that performed for infection localized to the toe, with clearly viable wound edges, and no suggestion of proximal infection. In this case, a gauze dressing is applied and the patient is maintained in a postoperative shoe until healed. A cane or walker is utilized for protected weight bearing.

In cases where the wound is left open, culture directed antibiotics should be administered for soft tissue or bone infection depending on the extent of the infection. Infectious disease service consultation is advisable. The open wound should be treated according to the surgeon's preferred protocol. If there is significant depth and/or drainage of the wound, you may contemplate the use of alginates or a negative pressure system. Packing should be sufficient to absorb excess drainage, but not aggressive enough to interfere with wound contraction. The foot should be protected from full weight bearing during this time with the appropriate gait-assistive device.

Once healing has been achieved, the patient should have a prescription for protective foot gear. If there is evidence of pressure keratosis developing adjacent to the ray resection site, the patient should be seen in clinic as necessary to pare the callus in order to prevent transfer ulceration.

Complications

Persisting infection is rare if the wound was adequately debrided at the time of the ray resection. However, if residual infection is suspected, follow-up surgical debridement should be done. Wound failure may be owing to inadequate healing parameters, such as impaired blood flow or abnormal serum albumin. Such metabolic wound failures may require more proximal amputation to obtain healing.

The most common late complication of ray resection is transfer lesion and reulceration. If pressure keratosis cannot be managed with debridement and prescription shoes, then resection of

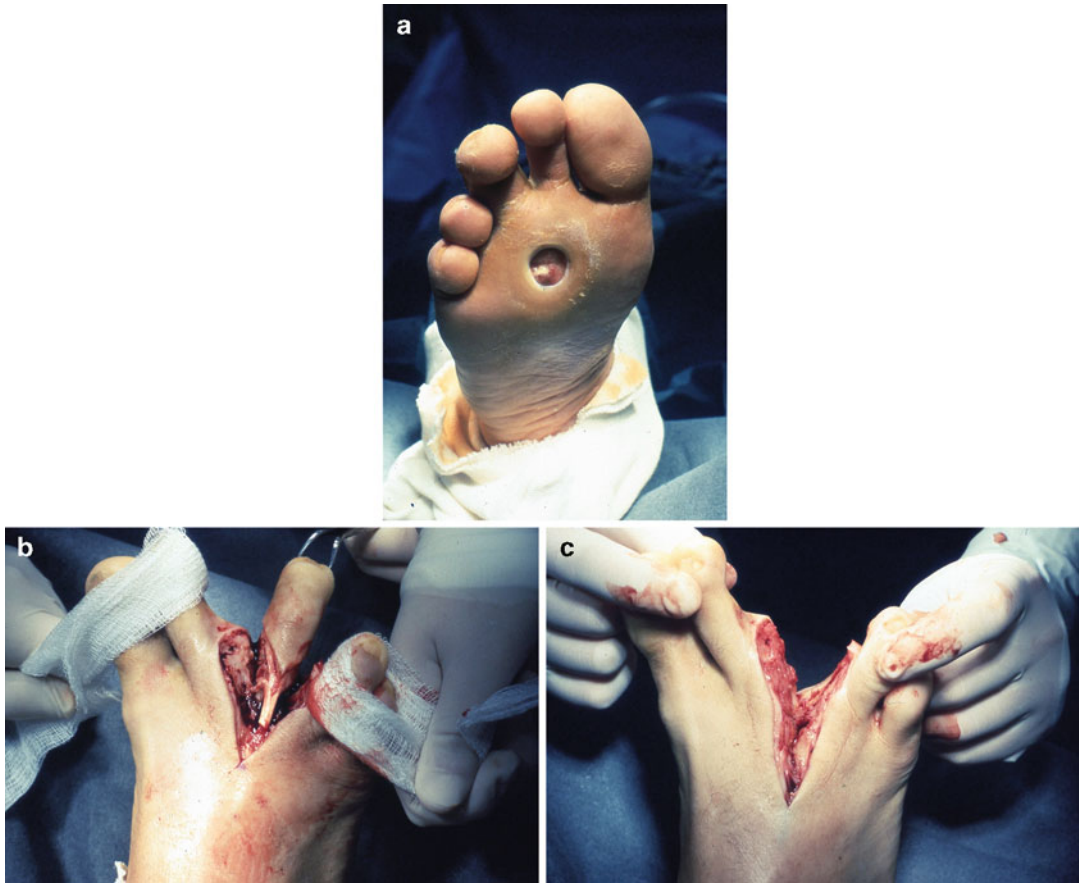

Fig. 22.5 (**a**) Plantar third metatarsal head ulcer. (**b**) Dorsal skin incision. (**c**) Patient after third ray amputation. Note that the plantar ulcer was also excised

the remaining metatarsal heads or more proximal amputation may become necessary [27].

Transmetatarsal and Lisfranc Amputation

Indications

The indications for amputation in a diabetic foot include irreversible necrosis of a significant portion of bone or tendon, uncontrollable infection, or intractable pain. If ulceration is present for a prolonged period of time, not responsive to nonsurgical treatment, and is causing significant disability, amputation of the ulcerated part may be a necessary step to rehabilitation. If the amputation is to be at the level of the toes, foot, or ankle, attention should be directed at well-established vascular and metabolic parameters to assure a reasonable chance for healing success.

McKittrick et al. [28] advocated the transmetatarsal amputation in 1949 for infection or gangrene of the toes in diabetic patients. Wagner, in 1977, subsequently recommended this amputation for use in patients with diabetic foot complications [29], advocating preoperative vascular review. He advised that Doppler studies demonstrating an ankle-brachial artery index greater than 0.45 could predict healing of the procedure with 90% accuracy. The authors' group reviewed 64 transmetatarsal and Lisfranc amputations in 1986 [30]. These amputations were performed for gangrene of the forefoot or forefoot ulcers recalcitrant to nonsurgical attempts at healing. Their results indicated that patients with Doppler

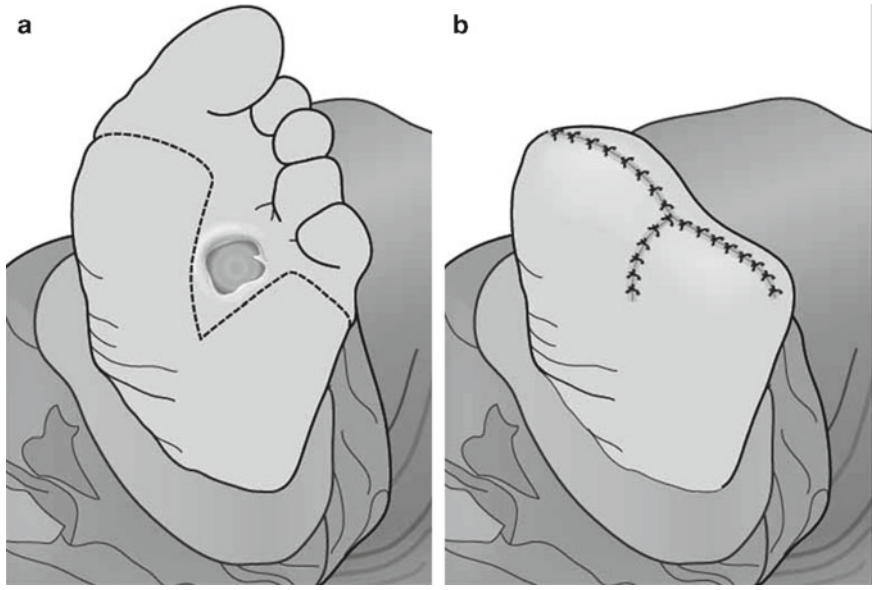

Fig. 22.6 (**a**) The Sanders' technique for plantar flap revision with transmetatarsal amputation in the presence of a distal plantar ulcer. (**b**) The margins of the ulcer site are then approximated with closure as shown

ankle-brachial artery index above 0.5, combined with serum albumin levels greater than 3.0 g/dl and TLC greater than 1,500/cm^3, healed at a rate of 92%. Those patients lacking one or more of these three indicators healed at a rate of 38%.

As stated earlier, amputation of a single toe or metatarsal may be successfully performed for patients with a localized ulceration if preoperative healing indices are satisfactory. However, even if early healing is achieved, there can be significant transfer ulceration following such procedures leading to later complications [26].

This experience suggests that transmetatarsal amputation may be a more definitive procedure for the management of forefoot ulceration. Transmetatarsal amputation may be considered for patients with more than one ulceration or site of necrosis of the forefoot. Likewise, this procedure may be considered in cases with a significant nonhealing ulceration and other foot deformities that are likely to lead to subsequent ulcer. However, transmetatarsal amputation, in itself, does not assure that no further ulceration of the foot is likely.

In our long-term review of midfoot amputations including transmetatarsal and Lisfranc procedures, 9 out of 64 feet sustained new ulcerations within the first year after healing the primary procedure [31]. The source of these ulcerations included hypertrophic new bone formation and subsequent varus or equinus deformity. These dynamic deformities occurred more in Lisfranc amputations, where muscle imbalance was likely to occur because of the loss of the attachments of the peroneals and extensors.

Plantar ulceration under the metatarsals may deter the surgeon from a transmetatarsal amputation, favoring a more proximal, yet more poorly functional, procedure because of the inability to preserve a long plantar flap for closure of the procedure. However, Sanders has demonstrated that a V-shaped excision of the ulceration, with the apex proximal and the base at the junction of the dorsal and plantar flaps, allows conversion of the wound from a simple transverse incision to a T-shaped closure [32]. This produces a longer, ulcer-free flap that can be closed over a transmetatarsal procedure, rather than requiring a more proximal Lisfranc operation to eliminate the plantar ulcer.

The specific indications for transmetatarsal amputation remain similar to McKittrick's, ulcer or gangrene of the toes. Thanks to Sanders plantar flap modification (Fig. 22.6), metatarsal head

ulceration is also an appropriate indication for this procedure, when not responding to nonsurgical treatment. Ulceration or infection of a single toe may be treated with an isolated ray resection, understanding a risk of transfer ulceration. If that risk is increased by obvious ulcerative deformity in other parts of the foot, then transmetatarsal or the slightly more proximal Lisfranc amputation becomes more appropriate. All of these procedures are most likely to heal when albumin, TLC, and arterial inflow meet recognized minimal standards described above. Before definitive midfoot amputation, acute infection should be stabilized by incision and drainage, debridement, or ray resection. Residual infected tissue present at the time of the definitive procedure can be expected to compromise success, and should be eliminated in a staged procedure, if necessary. If these criteria cannot be met, then higher amputation may be more appropriate.

Technique

This procedure can be performed with monitored anesthesia care, and spinal or ankle block. General anesthesia is rarely necessary. Appropriate medical clearance should be obtained regarding glycemic management and cardiovascular risks.

The transmetatarsal and Lisfranc amputations differ in technique mainly at the point of detachment of the forefoot from the hindfoot. The transmetatarsal procedure is osteotomized through the metatarsal bases, leaving the insertion of tibialis anterior, peroneus longus, and peroneus brevis intact. The metatarsal osteotomy should be performed through the proximal metaphysis in order to avoid long plantar metatarsal shafts and irregular parabola that might later result in plantar stump ulceration. The Lisfranc amputation requires disarticulation at the metatarsal-cuneiform and -cuboid joints, resulting in loss of the tendon insertions mentioned previously. The writer has made occasional attempts to preserve the base of the fifth metatarsal and peroneus brevis insertion, but this is not always practical.

The procedure begins with a dorsal incision across the metatarsal bases, from the medial to the lateral side of the foot, deferring the plantar incision for the time being. If no tourniquet is used, staging the incision like this avoids dealing with bleeding from both the top and bottom of the foot at the same time. The incision is carried to bone through the dorsal tendons and neurovascular structures. Significant vessels, such as dorsalis pedis, are identified and ligated. The periosteum of the metatarsal bases is incised and reflected using an elevator to expose either the site of the intended osteotomy or the metatarsal-tarsal articulation.

If a transmetatarsal amputation is to be performed, the osteotomies are now initiated. Using a power saw, the first metatarsal is cut, directing the plane slightly medially and plantarly. The second, third, and forth metatarsals are cut, taking care to produce a smooth parabola, leaving no residual metatarsal particularly longer than the adjacent bone. The fifth metatarsal is cut last, directing the plane slightly lateral and plantar. At this point, the plantar incision is made, initiated at a 90° or less angle to the dorsal incision, carried distally to the sulcus, around the metatarsal heads, and then posteriorly along the lateral side of the foot to the fifth metatarsal base. The incision should be carried to bone as much as possible. If plantar metatarsal head ulceration is present, it should be excised using a V-shaped wedge, directing the apex proximally and the base distally at the level of the distal transverse incision. When this is closed, it results in a T-shaped flap.

The metatarsals may now be lifted from the plantar flap from proximal to distal, dissecting along the metatarsal shafts in order to preserve as much of the soft tissue structures in the plantar flap as possible. The remaining distal attachments of the metatarsal heads are cut, and the forefoot is removed. Significant vascular structures should be ligated. The entire wound should be thoroughly irrigated. Remaining fibrous, ligamentous, and exposed tendinous structures should be cleanly cut from flap. Minimal debulking of the remaining intrinsic muscle structures may be

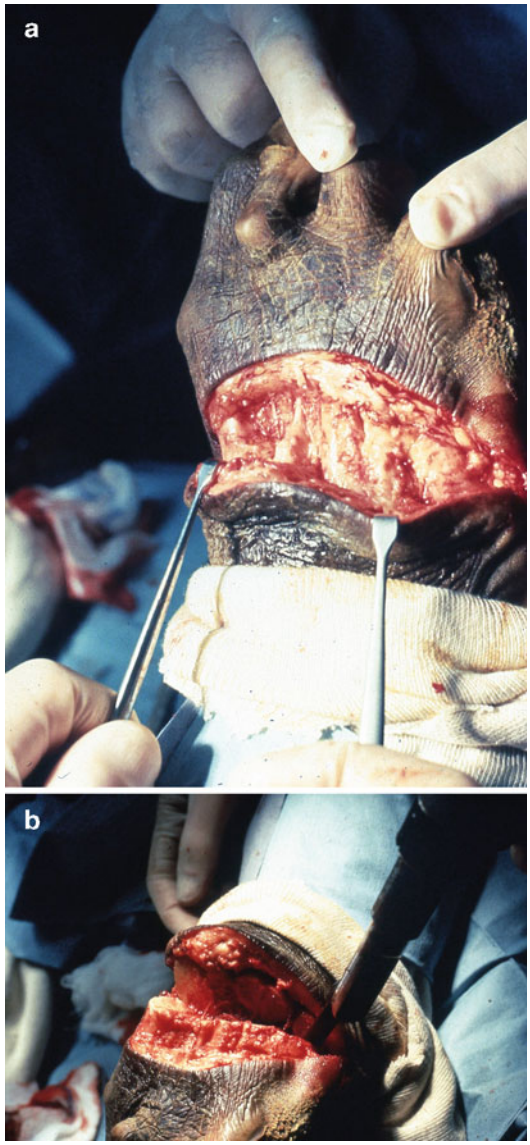

Fig. 22.7 (**a**) Dorsal incision with exposure of metatarsal. (**b**) Proximal metatarsal osteotomies to provide sufficient soft tissue coverage

performed if necessary to obtain approximation. However, as much of the viable tissue of the plantar flap as possible should be preserved (Figs. 22.7 and 22.8).

The technique is similar for a Lisfranc amputation, except that the metatarsal cuneiform and cuboid articulations are detached instead of the metatarsal osteotomy. The first cuneiform is invariably long, and needs to be ronguered or cut proximally to a smooth parabola with the remaining metatarsals. This cut should be directed slightly medially and plantarly. Articular cartilage from the remaining tarsals is ronguered to bleeding cancellous bone. Since adapting Sanders' plantar flap technique, the writer performs very few Lisfranc procedures because of the obvious functional disadvantage of varus and equinus associated with this procedure. If a Lisfranc is the only option, tibialis anterior is released from the medial side of the first cuneiform and a percutaneous tendo-Achilles lengthening is performed.

Prior to closure, the wound should be thoroughly irrigated. If a tourniquet is used, it should be released and significant hemorrhaging vessels ligated. Because the procedure leaves relatively little dead space, drains are rarely necessary. The wound is closed in two to three layers, starting with sutures placed in the middle of the planar flap musculature and approximated to the intermetatarsal or intertarsal ligamentous structures. Then, subcutaneous sutures are passed from the distal deeper layers of the flap to the dorsal retinaculum. Finally, the skin is closed with mattress or simple interrupted sutures of 3–0 nylon as needed to obtain a satisfactory incision line.

Postoperative Care

Mild compression and protection of flap from tension are the writer's objectives in immediate postoperative wound care. In order to accomplish this, a soft gauze roll dressing is applied from the foot to the ankle. Moderated compression is applied, with minimal force directed from plantar to dorsal in order to protect the plantar flap from undue stress on the incision line. Then, two to three layers of cast padding are applied from the foot to the tibial tuberosity, maintaining the foot and ankle in neutral position, neither dorsiflexed nor plantar flexed. Finally, several layers of $5 \times 30''$ plaster of Paris splints are applied posteriorly from the tip of the residual foot to the calf, distal to the knee. The splints are wrapped

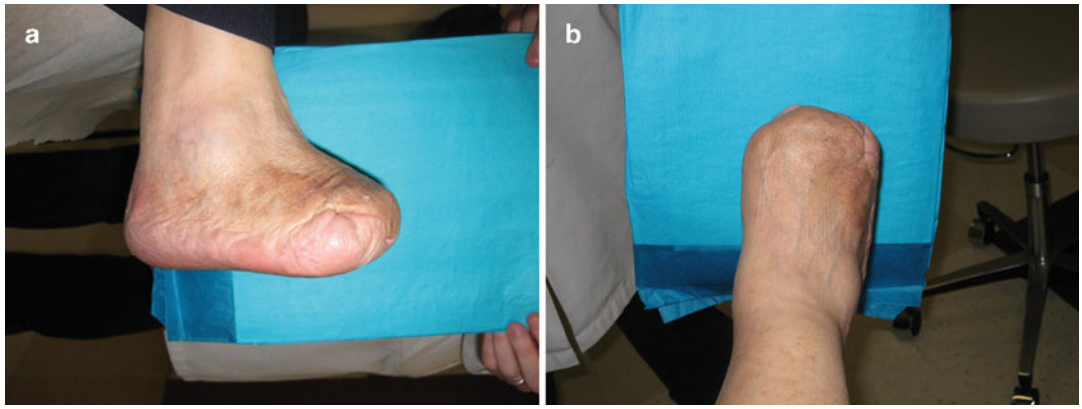

Fig. 22.8 (**a**, **b**) Healed transmetatarsal amputation without equinus, lateral and DP view

with another two layers of cast padding, and an ace wrap secures the entire dressing. This resembles a Jones dressing, protecting the wound from any contusions and from any dorsal or plantar tension.

This dressing is left in place for approximately 48 h before the wound is inspected. A similar dressing is maintained for 2–4 weeks until the incision line is clearly stable. During this time, the patient is instructed in the use of crutches, a walker, or wheel chair with leg elevation. Little or no weight bearing on the operated foot is allowed until the wound is clearly stable and free of risk of major dehiscence. Occasional superficial dehiscence may occur, especially in high-risk patients. This is treated like any other grade I ulcer with cleansing, debridement, and topical wound care measures until healed. Major postoperative dehiscence, infection, or necrosis of the plantar flap will likely require revision surgery.

Complications

Wagner has stated that distal amputations can be expected to heal up to 90% of the time in diabetics who exhibit adequate circulation as determined by Doppler examination demonstrating ankle-brachial artery index of 0.45 or better [29]. The authors' group confirmed that healing could be achieved in over 90% of patients with diabetes undergoing midfoot amputation if ankle-brachial artery index is over 0.5, serum albumin is greater than 3.0 g/dl, and TLC is over 1,500/cm^3 [30]. However, we have also noted that up to 42% of midfoot amputations may suffer some form of complication, even though the majority may ultimately heal their surgical wounds [31]. The complications include early wound dehiscence and late reulceration, which can be treated successfully to result in limb salvage in most cases. Patients most likely to suffer wound dehiscence include those with marginal vascular indices and low serum albumin. This is especially true in renal failure patients. These prognostic indicators should be taken into consideration in preoperative planning and discussed with the patient. Those at high risk for failure may be better served by a higher amputation more likely to heal with one operation.

Biomechanical abnormality resulting from muscle imbalance can result in dynamic varus, producing lateral foot ulceration. This is particularly true in Lisfranc amputations because of the varus pull of an unopposed tibialis anterior. Tibialis anterior tendon transfer in some cases can successfully treat this. Armstrong and associates [33] noted that bone regrowth after partial metatarsal amputation resulted in a significantly increased risk of reulceration. This regrowth was likely to occur in metaphyseal procedures, in males, when manual bone-cutting equipment was

utilized. In our experience, these reulcerations can be treated with aggressive exostectomy of the underlying bone and standard subsequent wound care.

Long-Term Follow-Up Needs

Patients with a history of ulceration remain at high risk for reulceration, even after the foot has been returned to grade 0 by a surgical procedure. The patient who has undergone any form of partial foot amputation should be placed in a high-risk foot clinic for regular follow-up visits. Both short- and long-term complications have been recognized. Even though the benefits of distal limb salvage are well accepted, biomechanical review and management visits must be included in aftercare for the amputation to be successful [34]. Early on, the wound should be protected with a posterior splint or cast and limited weight bearing. Rehabilitation should include crutch or walker training, if feasible. If the patient cannot use gait-assistive devices, a wheel chair with leg lift and instruction in wheel chair mobility and transfer techniques should be provided. These protective measures should be continued until wound is clearly healed.

Later, protective foot care or even a plastazote-lined ankle–foot orthosis may need to be prescribed for adequate protection. Although many patients may function well with an oxford shoe and anterior filler, others may need more elaborate orthotic management. Custom-made short shoes, rocker bottom shoes with a steel shank and anterior filler, or conventional shoes with an ankle–foot orthosis have all been advocated. Each patient should be observed carefully as they return to full ambulation to determine the need for orthotic management. Computer-assisted pressure mapping may be helpful in determining the success of any device in off-loading residual pressure points. If keratotic lesions should develop, these should be considered preulcerative and debrided regularly before ulceration can occur [35–37].

Transmetatarsal and Lisfranc amputations have the benefit of improved function and patient acceptance over higher amputation for individuals suffering from serious forefoot infection, ulceration, or gangrene. However, these operations must be recognized as high-risk procedures. Nevertheless, with appropriate preoperative planning, meticulous surgical technique, protective postoperative care, and long-term follow-up, midfoot amputations can be successful limb salvage techniques for most patients undergoing these procedures.

Chopart Amputation

Indications

Francoise Chopart described disarticulation through the midtarsal joint while working at the Charitable Hospital in Paris in the 1800s [38]. The operation has been thought to have limited applications because the residual foot is susceptible to progressive equinovarus deformity. The Chopart amputation is gaining new favor because the length of the limb is retained and the potential complications of the procedure can be successfully addressed. Combining ankle fusion with hindfoot amputation allows apropulsive ambulation with a modified high-topped shoe [38–41].

Amputation levels are usually chosen on the basis of tissue viability and residual limb function. A Chopart-level amputation may be considered when the longer transmetatarsal or Lisfranc amputation level is not an option because of the extent of forefoot tissue necrosis. Half of all patients undergoing an initial nontraumatic amputation will likely require an amputation of the contralateral limb [42]. As discussed earlier, there is a higher metabolic requirement for ambulation in those patients who undergo more proximal amputations. Therefore, the decision on amputation level should attempt to maximize the patients' mobility and independence by preserving length whenever possible, thus making the Chopart amputation useful in cases where more distal foot procedures are not feasible.

An open Chopart amputation is useful to provide resection of grossly infected forefoot structures, as a stage-I procedure, anticipating a higher

definitive procedure, such as a Boyd or Syme's amputation. The open Chopart amputation procedure disarticulates the foot at the level of the calcaneocuboid and talonavicular joints, leaving the articular surfaces intact. The proximal spread of infection may be less likely with the cancellous spaces unopened [43]. During the open Chopart procedure, care must be taken to visualize and resect all necrotic and/or nonviable tissue. Compression of the limb proximal to the open amputation site is done manually to identify purulent drainage from the compartments of the leg. If purulence is expressed with compression, then the affected compartment must be incised and irrigated to provide adequate drainage. Once the acute infection is resolved and the healing parameter indices are suggestive of healing, the open Chopart may be revised to a definitive amputation. If the surgeon anticipates that the acute infection may be stabilized and healing is anticipated at the Chopart level, then care must be taken to retain sufficient soft tissue to provide coverage of the residual foot.

The prerequisite for a definitive Chopart amputation is that the plantar heel pad and ankle/subtalar joint articulations are not compromised [44]. A definitive Chopart amputation is considered if the forefoot infection extends proximal to the metatarsal bases and neither a transmetatarsal nor a Lisfranc amputation can be salvaged. Reyzelman et al. [45] suggest that a Chopart amputation is more advantageous than a short transmetatarsal or a Lisfranc amputation because it does not disrupt the transverse arch of the foot. The disruption of the transverse arch creates an overpowering of the tibialis anterior, tibialis posterior, and gastrocnemius muscle to the peroneus brevis muscle. The muscle imbalance created in the short transmetatarsal or Lisfranc amputation may lead to a varus rotation of the residual foot. A frontal plane rotation of the weight-bearing surface of a Chopart amputation is less likely to occur, unless the calcaneus or ankle is structurally in varus [46]. The Chopart amputation does, however, lead to an equinus deformity because of the unopposed pull of the Achilles tendon. An Achilles lengthening and/or performing a tibialis anterior transfer at the time of the definitive closure may address this.

Technique

The dorsal incision begins from the tuberosity of the navicular extending dorsolateral to the mid cuboid level. The medial and lateral incisions are carried distally to the mid shaft level of the first and fifth metatarsals and continued transversely at this level along the plantar aspect of the foot. These incisions form a "fishmouth" creating a dorsal and plantar flaps. The incisions are deepened to expose the talonavicular and calcaneocuboid joints. The tibialis anterior should be identified and preserved for later transfer to the talar neck. The remaining soft tissue structures are incised to complete the disarticulation of the forefoot from the rearfoot. The articular cartilage of the talus and calcaneus should be resected creating a flush surface when the definitive procedure is being performed. The tibialis anterior tendon may be attached to the talar neck by the surgeon's preferred method. If a tourniquet has been utilized, it is deflated and hemostasis is achieved. Once you have completed deep closure, the skin edges are then reapproximated and secured, ensuring no excessive tension. A drain is necessary only if there is significant loose soft tissue, or if excessive bleeding is anticipated, to prevent hematoma formation. After the surgical site has been primarily closed, the Achilles tendon is lengthened by the surgeon's preferred method to limit later equinus deformity. A sterile compressive dressing and a posterior splint are applied to the lower extremity, as was described for transmetatarsal/Lisfranc amputation.

Postoperative Care

The patient is maintained non-weight bearing in a posterior splint or below-knee cast until the wound is healed for up to 6 weeks if necessary. The Chopart amputee without equinus is capable of ambulating in an extra inlay depth shoe with a forefoot filler but functions best with a polypropylene solid AFO prosthesis with a foam filler [43]. The prosthesis helps to eliminate or minimize the pistoning motion of the distal amputation in a normal shoe. If the Chopart amputee has an equinus, then he or she should be fitted for a clamshell prosthesis (Fig. 22.9 Chopart) [47].

Complications

Infection or wound failure is not a complication specific to the Chopart amputation but is more likely if performed on patients who did not meet the generally accepted vascular and nutritional parameters described earlier. Care must be taken to fashion the flaps to provide adequate coverage for the residual foot without soft tissue being secured under excessive tension, as this may lead to wound dehiscence and/or devitalization. Equinus deformity can still occur even if Achilles lengthening is performed. The development of a plantar ulceration in a plantarflexed residual foot is a common occurrence and may lead to revision surgery. As always, close postoperative follow-up and early intervention may minimize these problems.

In spite of these shortcomings, the Chopart amputation remains useful as an early incision and drainage procedure to stabilize acute infection. It is also useful as a definitive procedure in select cases because of its advantage of limb length and tissue preservation.

Transmalleolar Amputation: The Syme's Procedure

Indications

Hindfoot amputation, to be successful, must produce a reliable result with a long-lasting and functional residual limb. Chopart's amputation at the talonavicular and calcaneal-cuboid joints creates significant muscle imbalance frequently resulting in ankle equinus and ulceration. The Boyd amputation has also been advocated [48]. This procedure involves fusion of a portion of the calcaneus to the distal tibia. The advantage is that the heel pad remains well anchored to the calcaneus. An additional problem becomes evident in attaining union of the tibia to calcaneus. There may also be difficulty in prosthetic fitting.

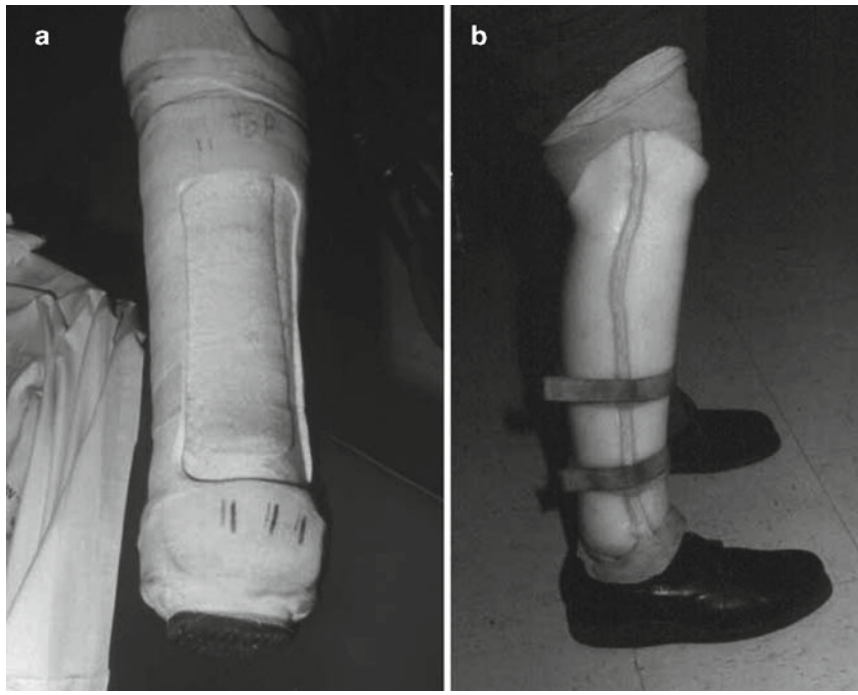

Fig. 22.9 (**a**) A fiberglass cast with a distal rubber bumper and a medial window is used as a temporary prosthesis to allow early ambulation for the Syme's amputation patients. (**b**) A thermoplastic variation of a temporary prosthesis with a prosthetic foot attached. In a patient with very limited ambulation, this may also serve as permanent prosthesis. (**c**) A variety of Chopart prostheses have been advocated. This prosthesis has a posterior closure

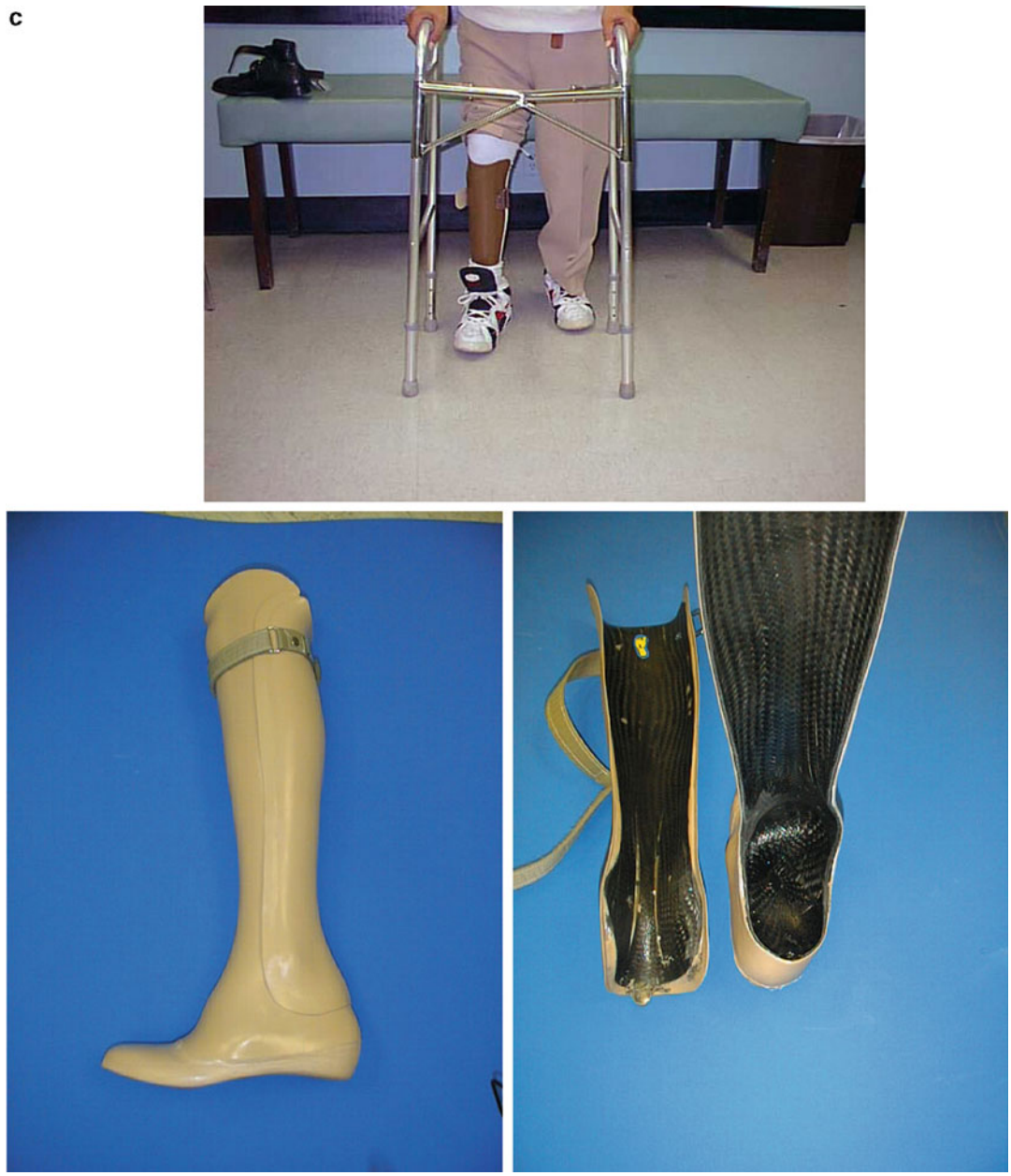

Fig. 22.9 (continued)

The residual limb remains long and there is inadequate space to place a dynamic-response prosthetic foot without raising the height of the contralateral limb to compensate for this addition. It is unknown whether this height difference results in gait problems for the diabetic patient.

The Syme's amputation is performed through the malleoli and results in physiologic weight bearing throughout the residual limb. The fat pad takes load directly and transfers this directly to the distal tibia [49]. With the use of dynamic-response feet, this amputation level results in

decreased energy expenditure with ambulation compared to higher procedures or midfoot amputation [50–53]. Contraindications for this procedure include local infection or gangrene at the level of the amputation, and inadequate nutritional and vascular parameters to sustain distal healing. Healing may achieved using this procedure with serum albumin levels as low as 2.5 g/dl [49]. Heel ulceration has been considered a contraindication to a Syme's procedure in the past. However, an anterior flap may be useful in patients with a nonviable heel pad [52, 54]. A long-term review of this procedure modification in a significant series of patients has not yet been performed.

Procedure

The incision is placed anteriorly across the ankle mortise and then in a stirrup fashion across the anterior heel at the level of the malleoli. The incision is deepened at the anterior ankle and the ankle capsule is incised transversely. The ankle ligaments are released sharply and the talus is displaced anteriorly in the mortise. A bone hook is placed into the talus and used to anteriorly distract the talus so that soft tissues may be freed from the talus and the calcaneus. Care is exercised at the posterior calcaneus to prevent buttonholing of the skin while releasing the soft tissues. Once free, the residual foot is removed from the wound and the wound is thoroughly irrigated. The residual tendons are gently distracted 0.5–1 cm and sectioned. If needed, the anterior ankle vessels may be ligated with appropriate suture. Anterior and posterior margins of the distal tibia may require debridement to diminish excessive spurring. Two drill holes may be placed in posterior tibia and/or the anterior tibia. A heavy absorbable suture (0) may be utilized through the drill holes to anchor the plantar fascia to the distal tibia. The anterior aspect of the residual plantar fascia is sutured into the anterior ankle capsule and the subcutaneous tissues and skin are closed in layers. A medium hemovac drain is placed prior to closure. A posterior splint or a short leg cast is placed. The drain is removed 24–48 h after surgery.

Postoperative Care

The patient may begin assisted/partial weight bearing at 3–5 days and is maintained in a short leg cast for 3–6 weeks. The patient is then advanced to a fiberglass cast temporary prosthesis with a rubber bumper distally. Once the patient's limb has matured and there is minimal residual edema, the patient is fitted for a Canadian Syme's prosthesis with a dynamic-response foot (Fig. 22.10a, b). Full activity is resumed. The need for physical therapy gait training is unusual.

Complications

Healing rates for this level vary from 70 to 80%. Early complications with the wound may occur in up to 50% of the patients. Most of these problems may be treated with local wound care, total contact casting, and culture-specific antibiotic therapy. Other problems include heel pad migration and new bone formation. Heel pad migration has become less frequent with anchoring of the fascia. Should new bone formation become significant or cause ulceration, exostectomy may become necessary [49].

Transtibial or Below-Knee Amputation

Indications

Individuals with transtibial amputation provide the largest population of patients that are capable of achieving meaningful rehabilitation and functional independence following lower extremity amputation. The most predictable method of obtaining a durable residual limb is with a posterior myofasciocutaneous flap [55]. This level takes advantage of the plastic surgical tissue transfer technique of a composite tissue flap without dissection between layers, thus minimizing the risk for devascularization of the overlying skin.

Procedure

The optimal tibial transection level to optimize functional ambulation is a tibial length of

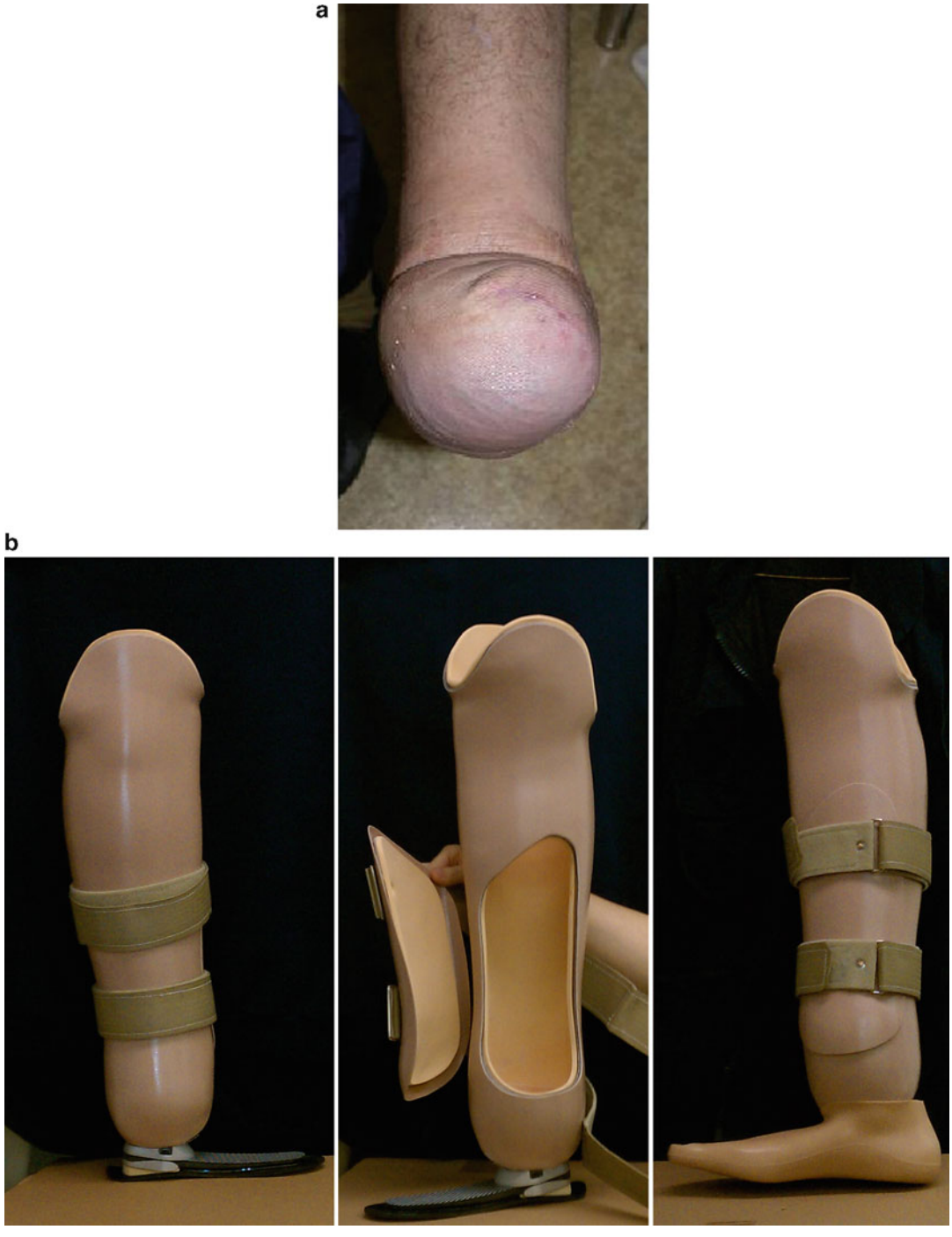

Fig. 22.10 (**a**) A well-performed Syme's amputation with tapered stump and heel pad. (**b**) Syme's prosthesis with and without prosthetic foot

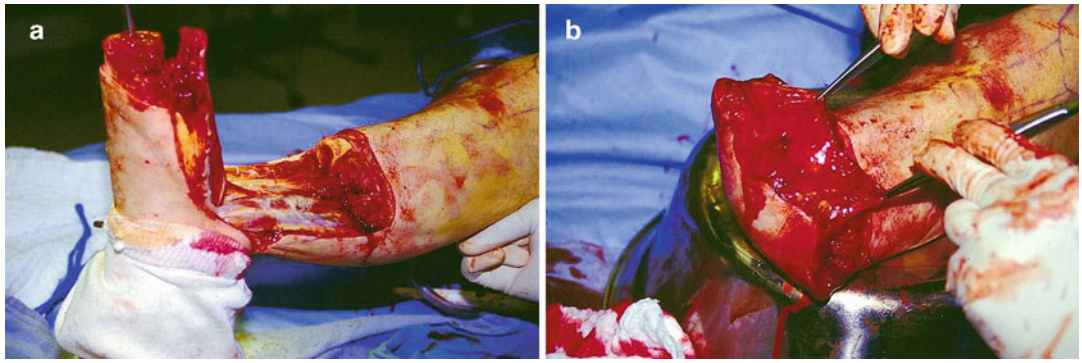

Fig. 22.11 (**a**, **b**) Posterior myofasciocutaneous flap used in transtibial amputation level

12–15 cm distal to the knee joint. The fibular amputation level in the past has been advised to be approximately 1 cm shorter than the tibia. In order to optimize the weight-bearing platform of the transtibial amputation stump, it is now felt that the fibula level should be just a few millimeters shorter than the tibia. The length of the posterior flap should be equal to the diameter of the limb at the level of the tibial transection level, plus 1 cm. A short "fishmouth" should be used on the anterior aspect of the stump to place the surgical scar in a better area for prosthetic fitting. The longitudinal component of the flap should range from one-third to one-half of the width of the limb, depending on the bulkiness of the leg. Thinner limbs with more tenuous blood supply are better performed with a width of approaching 50%, while the amputation stump in obese patients are best created with a width of approximately one-third the diameter (Figs. 22.1 and 22.11a).

The anterior corner of the tibia should be beveled to decrease the shear forces on the anterior-distal aspect of the amputation stump. Historically, the posterior fascia of the gastrocnemius muscle has been sutured to the end of the anterior compartment fascia and the periosteum of the tibia. In order to create a better soft tissue envelope and enhance weight bearing, it is now advised to use a version of the "extended posterior flap" as described by Smith et al. [56]. In this method, the posterior gastrocnemius fascia is sutured to the anterior compartment of the leg and the periosteum of the tibia at a level of 1–2 cm proximal to the bony transection.

Postoperative Care

Postoperatively, a rigid plaster dressing is applied [57]. Weight bearing with a prosthesis is initiated at 5–21 days, based on the experience and resources of the rehabilitation team (Fig. 22.12).

Knee Disarticulation

Indications

Knee disarticulation is generally performed in patients with the biologic capacity to heal a surgical wound at the transtibial level, but they are not projected to walk with a prosthesis [58, 59]. In selected patients, it provides an excellent direct load transfer residual limb for weight bearing in a prosthesis. In limited household walkers or in feeble amputees with limited ambulatory capacity, this level takes advantage of the intrinsically stable polycentric four-bar linkage prosthetic knee joint. The enhanced inherent stability of this prosthetic system decreases the risk for falls in this limited ambulatory population.

Procedure

The currently recommended technique takes advantages of the accepted transtibial posterior myofasciocutaneous flap [60]. The skin incision

Fig. 22.12 Standard below-knee total surface-bearing prosthetic socket and silicone suspension sleeve

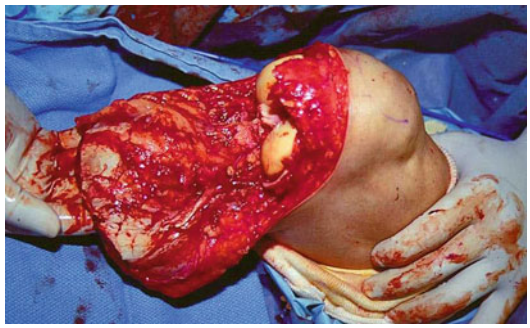

Fig. 22.13 Posterior myofasciocutaneous flap used in knee disarticulation amputation

is made transversely midway between the level of the inferior pole of the patella and the tibial tubercle, at the approximate level of the knee joint. The length of the posterior flap is equal to a diameter plus 1 cm (as with transtibial). The width of the flap again varies with the size of the patient, ranging between the posterior and middle thirds of the circumference of the leg (Fig. 22.13). The patellar ligament is detached from the tibia, and the capsule of the knee joint is incised circumferentially. The cruciate ligaments are detached from the tibia. A full-thickness posterior myofasciocutaneous flap is created along the posterior surface of the tibia. The soleus muscle is generally removed, unless it is needed to provide bulk. The gastrocnemius muscle is transected at the level of the posterior skin incision, with no creation of a tissue plane between the muscle and skin layers. The patellar ligament is then sutured to the distal stumps of the cruciate ligaments with nonabsorbable suture. The posterior gastrocnemius fascia is then sutured to the patellar ligament and knee joint retinaculum retained. The skin is reapproximated by suture or skin staples, and a rigid postoperative plaster rigid dressing.

Postoperative Care

Early weight bearing with a preparatory prosthesis or pylon can be initiated when the tissues of the residual limb appear secure. A locked knee or polycentric four-bar linkage prosthetic knee joint can be used, depending on the walking stability of the patient (Figs 22.14a).

Transfemoral or Above-Knee Amputation

Indications

Gottschalk has clearly shown that the method of surgical construction of the transfemoral residual limb is the determining factor in positioning the femur for optimal load transfer [61]. Standard transfemoral amputation with a fishmouth incision disengages the action of the adductor

Fig. 22.14 (**a**) Knee diarticulation polycentric four-bar linkage knee joint with preparatory prosthetic. (**b**) Knee disarticulation amputee with polycentric four-bar linkage knee

musculature. By disengaging the adductor muscles, the femur assumes an abducted, nonfunctional position. This relative functional shortening of the abductors produces an apparently weak abductor gait pattern. By using an adductor-based myocutaneous flap, the adductor muscles can be secured to the residual femur, allowing the femur to be appropriately prepositioned within the prosthetic socket [62].

Procedure

In order to accommodate a prosthetic knee joint, the optimal bone transection level is 12–15 cm proximal to the knee joint. The soft tissue envelope is composed of a medial-based myofasciocutaneous flap. The flap, including adductor magnus insertion, is dissected off the femur. After securing hemostasis and cutting the bone, the adductor muscles are secured to the lateral cortex of the femur via drill holes, under normal resting muscle tension. The anterior and posterior muscle flaps are also secured to the residual femur via drill holes. Careful attention is taken to secure the muscles to the residual femur with the hip positioned at neutral flexion–extension so as to avoid an iatrogenic hip flexion contracture, so often produced by repairing the soft tissues with the residual limb being propped on bolsters during wound closure.

Postoperative Care

An elastic compression dressing is applied, and weight bearing with a preparatory prosthesis is initiated when the wound appears secure (Fig. 22.15).

Hip Disarticulation

Few hip disarticulation amputees become functional prosthetic users. Whether sitting in a chair or "sitting" in a prosthetic socket, the weight-bearing platform can be enhanced by retaining the femoral head within the socket.

Rehabilitation

Surgical amputation should be the first step in the rehabilitation of the patient. Thus, the rehabilitation process should be initiated before the actual amputation surgery, whenever possible. The rehabilitation team should have a reasonable expectation of the patients' ultimate rehabilitation potential. When one measures results from an ambulatory perspective or from a measure of achieving activities of daily living, amputees are

Fig. 22.15 Hybrid transfemoral prosthetic socket with modified quadrilateral shape and ischial containment

less functional or independent with more proximal-level amputees. Unilateral ankle disarticulation amputees walk and are functional at a level very comparable to their age and disease-matched counterparts. While 87% of transtibial amputees will be functional walkers at 2 years, 36% will have died [63]. Ambulatory knee disarticulation amputees fare somewhat less well from both ambulatory and independence perspectives. Very few diabetic, dysvascular transfemoral amputees, or bilateral amputees, will become functional walkers.

Regardless of the amputation level, the first step in regaining functional independence is transfer training leading. Many debilitated patients will not have the energy reserves, stamina, or strength to walk with a prosthesis. For these patients, the wheelchair will provide their method of ambulation.

Residual limb care in the early postoperative period can enhance, or detract from, good surgical technique. Specific wound care is related to the circumstances of the surgery. The use of rigid postoperative plaster dressings in transtibial or knee disarticulation amputations controls swelling, decreases postoperative pain, and protects the limb from trauma. The rigid plaster dressing is changed at 5- to 7-day intervals, with early postoperative prosthetic limb fitting and weight bearing being initiated between 5 and 21 days following surgery. Immediate postoperative prosthetic fitting should be reserved for patients with very stable, secure residual limbs. Generally, the residual limb of the transfemoral amputee is managed with a suspended compression dressing. Weight bearing with a prefabricated, or custom, prosthetic socket and training pylon can be initiated when the wound appears secure. With more proximal-level amputation, these multiple system-involved individuals are more likely to require walking aids, with almost all dysvascular diabetic amputees requiring the use of a walker or crutches for their limited range of walking.

Following achieving independence in transfer to the chair, the next step is functional ambulation with gait-assistive devices. The timing of allowing patients to bear weight and start prosthetic fitting will be dependent on the individual patient and the experience of the rehabilitation team. Generally, prosthetic fitting for major limb amputation is initiated at 2–6 weeks following surgery.

When the treatment team develops reasonable, realistic goals, patients are capable of achieving the highest level of functional walking compatible with their multiple organ system disease.

Conclusion

Partial foot amputations are frequently used to successfully accomplish limb salvage. If below-knee or higher amputation is required to achieve healing, many patients return to community

ambulation, still utilizing and stressing the remaining limb. Once any form of amputation has occurred, the patient must be considered at high risk for further amputation [32]. The principles of managing any high-risk foot must be applied, and regular review and management services are essential for preserving the salvaged and contralateral limb.

Patient education, shoe review with appropriate prescription or recommendation, and regular professional foot exams are the mainstay of any preventive program [35]. Regular follow-up must be initiated after healing has been accomplished. The patient should be instructed in regular self-foot exams and the effects of sensory neuropathy. Potentially ulcerative pressure points should be identified and accommodated with orthotics and/or shoes as needed. Recurring pressure keratosis should be acknowledged as a potential ulceration, and debrided as necessary to prevent the callus from becoming hemorrhagic or ulcerative. This may require intervals as little as every 4 weeks [33, 36].

It has been the authors' experience that no surgical procedure is effective, in itself, in preventing subsequent foot ulcers. The patient with any form of lower extremity amputation must be considered at high risk for further ulceration. Careful clinical follow-up, orthotic care, and debridement of chronic focal pressure keratosis are far more effective in preventing ulceration or further amputation than any operation.

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Part IV

Organization and Preventive Care

Organization of the Diabetic Foot Care Team

23

John M. Giurini and Frank B. Pomposelli Jr.

Abstract

Diabetes is a multifaceted disease characterized by a multitude of complications. Patients with diabetes present not only with lower extremity complications, i.e., peripheral vascular disease and ulcerations, but also with chronic renal disease, cardiac disease, or gastrointestinal disturbances. For this reason, a multidisciplinary team is essential to the management of these complications even when patients are admitted for seemingly unrelated conditions. Failure to recognize and manage these comorbid conditions can lead to prolonged hospitalizations and less than optimal outcomes.

This is not a new statement or concept. Clinical practice and reports strongly support the importance and efficacy of the team approach, whether it is for managing diabetic foot complications or other complications of diabetes.

Keywords

Historical perspective • Joslin-Deaconess foot center model

Diabetes is a multifaceted disease characterized by a multitude of complications. Patients with diabetes present not only with lower extremity complications, i.e., peripheral vascular disease and ulcerations, but also with chronic renal disease, cardiac disease, or gastrointestinal disturbances. For this reason, a multidisciplinary team is essential to the management of these complications even when patients are admitted for seemingly unrelated conditions. Failure to recognize and manage these comorbid conditions can lead to prolonged hospitalizations and less than optimal outcomes.

This is not a new statement or concept. Clinical practice and reports strongly support the importance and efficacy of the team approach, whether it is for managing diabetic foot complications or other complications of diabetes [1–3]. So, the question becomes how does one set up this multidisciplinary team and who should be involved?

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Historical Perspective

In 1952, Dr. Elliot Joslin started the world famous Joslin Diabetes Center. He immediately realized that if he were going to be successful in treating diabetes, he would need a team of specialists. These specialists would need to understand diabetes and its many complications. For lower extremity issues including infections and peripheral vascular disease, he selected Dr. Leland McKittrick, a renowned general surgeon. For the management of diabetic foot problems, he selected Dr. John Kelly who in 1928 became the first podiatrist admitted to the medical staff of a major medical center [4]. This constituted the earliest collaboration between vascular surgery and podiatry, a relationship that has continued into the present day.

From those early beginnings, the collaboration between vascular surgery and podiatry at the New England Deaconess Hospital has served as the model for nearly every wound care center currently in existence. Early collaboration consisted mainly of service-to-service consultation on challenging cases. In the case of vascular surgery, this consisted mainly of consultation for radical debridement of infected feet or amputation. In the case of podiatry, this consisted mainly of consultation for ongoing conservative management of neuropathic ulcers or preventative foot care.

As this collaboration matured, focus shifted from major limb amputation to limb salvage. Dr. McKittrick and his young associate, Dr. Frank Wheelock, recognized that not all diabetic patients suffered from peripheral vascular disease. In fact, infection in the presence of peripheral sensory neuropathy was the main reason diabetic patients underwent below-the-knee amputations. Recognition of this fact resulted in the popularity and feasibility of the transmetatarsal amputation. This procedure was popularized and described as a viable alternative to major limb amputation in diabetic patients by Drs. McKittrick and Wheelock. In his presentation at a major surgical meeting in St. Louis, Dr. McKittrick described how it was possible to amputate only the forefoot and leave diabetic patients with a stable foot for ambulation [5]. Because of this presentation and the collective experience of the surgeons of the Deaconess Hospital, the TMA became known as the "Deaconess operation."

However, the most significant event in the evolution of vascular surgery took place in the early 1980s when lower extremity revascularization took a major step forward. It was always observed that vascular disease in diabetic patients differed significantly from nondiabetics. The most common site of arterial blockage in patients without diabetes is in the iliac or superficial femoral arteries. The popliteal and tibial arteries are generally spared. In diabetic patients, however, the proximal vessels (iliac and superficial femoral) and pedal vessels (dorsalis pedis and posterior tibial) are spared while the vessels below the knee (outflow vessels) are diseased. This made doing a bypass around the blockage and into the pedal vessels possible. This was further facilitated by improved surgical instrumentation and imaging techniques.

It was also during the early 1980s that podiatry matured as a profession. More emphasis was paid to ways to alleviate plantar foot pressures resulting from abnormal foot structure and to prevent recurrence of ulcerations. Podiatrists at the New England Deaconess Hospital became frustrated by the recurrent nature of diabetic foot ulcers in spite of good preventative care in the form of orthoses, shoegear modifications, and regular diabetic foot visits. In the late 1970s and early 1980s, the podiatry team at the New England Deaconess Hospital began performing local limb-sparing foot procedures to eliminate these pressure points and reduce the risk of recurrent ulcerations. These were commonly performed procedures in the form of digital arthroplasties, metatarsal osteotomies, and metatarsal head resections. These early attempts did not go without some skepticism. In a famous exchange between a vascular surgeon and the Chief of Podiatry, the vascular surgeon was heard to tell the podiatrist during a weekly foot conference that "if the metatarsal osteotomy did not work, it will be the last surgical procedure podiatry would perform at the hospital." Fortunately, for podiatry and all future diabetic patients with ulcerations, the osteotomy did work. This signaled the beginning of limb salvage surgery and a strengthened bond and collaboration between vascular surgery and podiatry. Limb-sparing foot surgery following a

vascular procedure is now considered the routine standard of care and not the exception [6–8].

The Joslin-Deaconess Foot Center Model

While some form of the foot center has existed since the days of Dr. Elliott Joslin, the Joslin-Deaconess Foot Center was formally established nearly 20 years ago in recognition of the fact that management of the diabetic foot requires a team approach. Diabetologists, podiatrists, and vascular surgeons joined forces in what represented the earliest wound care center. The Foot Center allowed for management and coordination of care for diabetic foot ulcers, vascular disease, as well as medical management of diabetes.

One of the most common questions asked is "Who should care for the diabetic foot and be involved in the center?" The simple answer is anyone with an interest. In reality, the answer is more complicated than that. There are several phases to the care of the diabetic foot. There is the care of the acute problem, i.e., acute ischemia, acute infection, or acute Charcot deformity without ulceration. Then, there is the chronic problem, i.e., the chronic nonhealing ulceration either because of ischemia or severe deformity, chronic Charcot with deformity and with or without ulceration, or chronic osteomyelitis. There is also preventive diabetic foot care for those diabetic patients with early complications without significant deformities but who are at risk for deformities. Each of these phases will require a different set of specialists along the course of treatment.

One individual common to each of these stages is the podiatric physician. The podiatrist must be knowledgeable and well versed in all aspects of diabetic complications and foot care. This includes the evaluation and treatment of diabetic foot ulcerations and infections, recognition of vascular disease, and ability to recognize, diagnose, and treat the earliest manifestations of Charcot joint disease. This individual must also be capable of educating diabetic patients on the care of their feet as well as recognizing the earliest signs of trouble, i.e., early signs of infections and skin breakdown. The podiatrist should also possess the necessary surgical skills to perform limb-sparing procedures. In addition to the more common limb-sparing procedures (e.g., osteotomies, exostectomies, and metatarsal head resection), the podiatrists should at least be familiar with the technically more demanding reconstructive procedures performed for complex Charcot joint deformities. If they do not have the surgical training or skills to perform these procedures themselves, they are the best members of the team to identify an individual who does possess those skills.

Two of the most important functions of the podiatrist are education and prevention. The podiatrist should be capable of educating the diabetic patients and their families on such topics as preventative foot care, diabetic foot complications, recognition of diabetic foot problems, early treatment of these problems, and selection of shoegear. The podiatrist is involved in the prevention of foot complications both in the newly diagnosed diabetic patient as well as in the long-standing diabetic patient with well-established complications and deformities. In the majority of situations, diabetic patients are referred to the podiatrist for long-term management following lower extremity surgery. For this reason, it is recommended that the podiatrist serves as the gatekeeper for diabetic foot complications (Fig. 23.1). His/her ability to evaluate patients regularly and recognize problems early allows him/her to make referrals to the appropriate specialist in a timely manner which is often critical.

As previously stated, vascular surgery has gone through many changes as a profession. In Drs. McKittrick's and Wheelock's days, fellowships in vascular surgery were nonexistent. Today, with the complexity of vascular surgery procedures, vascular surgery fellowships are essential. In dealing with the vascular complications of the diabetic patient, today's vascular surgeon must be trained in both standard open bypass procedures as well as endovascular procedures. Many more vascular surgeons are performing endovascular procedures not only as diagnostic procedures but also as therapeutic procedures. These procedures are performed to improve lower extremity inflow in patients with proximal disease. However, the vascular surgeon must also be well versed in performing distal bypass procedures in those cases

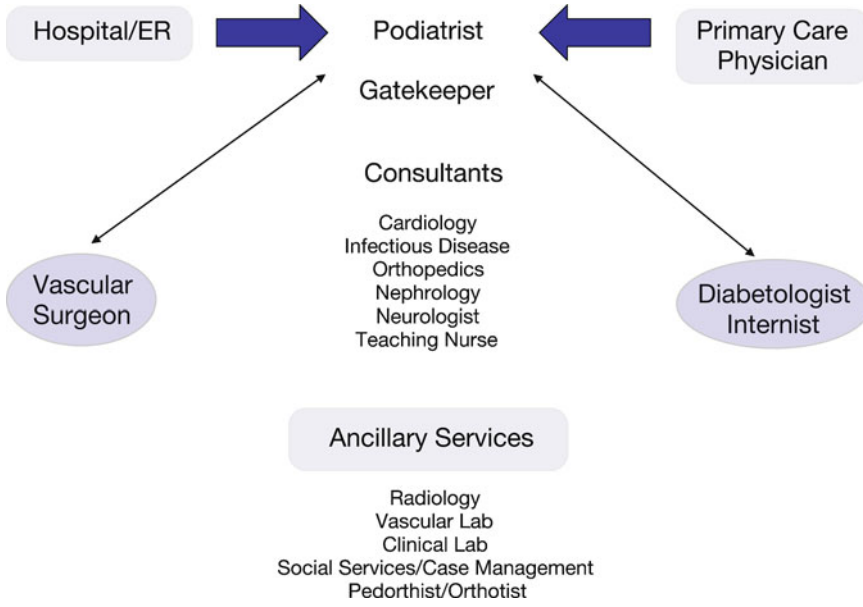

Fig. 23.1 One proposed model for a multidisciplinary diabetic foot clinic utilizes the podiatric physician as the gatekeeper while other specialists are readily available for consultations

where endovascular procedures cannot improve outflow disease into the foot.

In order to provide comprehensive treatment, even in the most complex patients, other key specialists must be readily available for consultation. These should include plastic surgery, orthopedic surgery, infectious disease, physical therapy, and prosthetists/orthotists. Each of these specialists is critical to the successful management of diabetic foot disorders.

Plastic surgery is an important member of the diabetic foot care team. On occasion, the podiatrist and the vascular surgeon will be faced with an ulceration that is so large and so deep that healing can take several more months, in spite of successful vascular intervention or reconstructive foot surgery. Therefore, a plastic surgeon knowledgeable and skilled in performing locally based advancement or rotational flaps can be a tremendous asset to the limb salvage team. His/her skills should also include the ability to perform free tissue transfers from a remote site to the foot when there is a lack of tissue available locally to make limb salvage feasible.

Traditionally, orthopedic surgeons have had little involvement in the management of the diabetic foot. In recent years, there has been renewed interest by the orthopedic community in this entity. In some cases, this has led to conflict (i.e., "turf battles") with well-trained surgical podiatrists. However, this need not be the case. In fact, with the podiatrists' understanding of foot structure, mechanics, and foot surgery and with the orthopedists' training in trauma, a collaborative approach between the two specialties is natural. Today's approach to reconstruction of complex Charcot joint deformities, especially of the hindfoot and ankle, requires knowledge of anatomy and biomechanics as well as the use of complex instrumentation to achieve limb salvage. In many cases, these procedures are best performed by a team of surgeons, regardless of degree designation.

The Diabetic "Foot" Floor

Success in the management and treatment of diabetic foot disorders is dependent on timely communication by all members of the management team. This communication is facilitated by the creation of a dedicated unit in the hospital for

patients with diabetic foot problems. This was recognized over 20 years ago by the vascular surgeons and podiatrists of the Deaconess Hospital. All patients with lower extremity vascular disease, foot infections, or nonhealing ulcerations are admitted to a common floor. This has several advantages. First, the vascular surgical team and the podiatry team make morning rounds at the same time every morning. Patients that are being comanaged by the teams are seen together. This assures that communication is timely and direct. It also assures that treatment plans are coordinated between the teams and that both teams are "on the same page" with regard to patient care. This is a fact that is not lost by the patient. The patient quickly recognizes that both teams are working as a unified team for the betterment of the patient.

The second advantage is that consultations can be readily obtained during rounds. Time is not lost waiting for phone calls or e-mails to be made or returned, orders to be placed, physicians to be notified and see the patient, and recommendations to be made. Physicians are consulted directly while on rounds, patients are seen immediately, diagnostics tests are reviewed or ordered, and recommendations are directly communicated to the referring physicians all in the same morning. This allows for immediate formation and execution of a treatment plan.

The third advantage is rounds can be conducted in a more efficient manner and more patients can be seen. Without a dedicated floor, physicians and residents spend an inordinate amount of time simply traveling from floor to floor, wing to wing, or building to building simply locating patients.

Finally, the fourth advantage of a dedicated unit is the ability to have assigned and appropriately trained nursing staff, case managers, and physical therapists to deal with the special requirements of diabetic patients with wounds. The nursing staffs on a dedicated floor are trained to recognize the early signs of infection or graft occlusion. They are trained in appropriate wound care and the performance of dressing changes. They are also familiar with the medical aspects of taking care of diabetic patients, such as insulin reactions, managing elevated blood glucose, chest pain, renal disease, special diets, or mobility issues.

Outpatient wound care centers incorporate several of these same characteristics. They are often run in a multidisciplinary fashion by podiatrists, vascular surgeons, general surgeons, or plastic surgeons. In some centers, these physicians are present simultaneously while at other centers they may have dedicated times. The centers are also staffed by dedicated wound care nurses who assist the physicians and serve as the bridge between physicians. Often times, they will provide direct communication among physicians, staffs, and patients to coordinate care. It is imperative that timely consultation and direct communication exist between all personnel regardless of how the center is structured. The Joslin-Deaconess Diabetic Foot Center is located in one building of the hospital while the Vascular Center is located in a different building. However, it is common practice that if a patient must see a podiatrist or a vascular surgeon for an immediate consult, that patient is seen and transported to the appropriate clinic.

The Ultimate Goal

When caring for the diabetic patient with a foot problem, it is important to always keep in mind and ask, "What is the ultimate goal?" The ultimate goal should always be total wound healing and limb salvage. Whatever barrier that stands in the way of achieving this goal must be dealt with and overcome. If it is a vascular issue, a vascular surgeon must be consulted and revascularization attempted. If it is an infection issue, an adequate debridement and drainage procedure must be performed. If blood sugars are poorly managed or controlled, endocrinology must be consulted to provide optimal management such that wound healing can be maximized. All of this must be performed in an environment where egos do not get in the way. There is no place for turf battles when it comes to the management of diabetic foot problems.

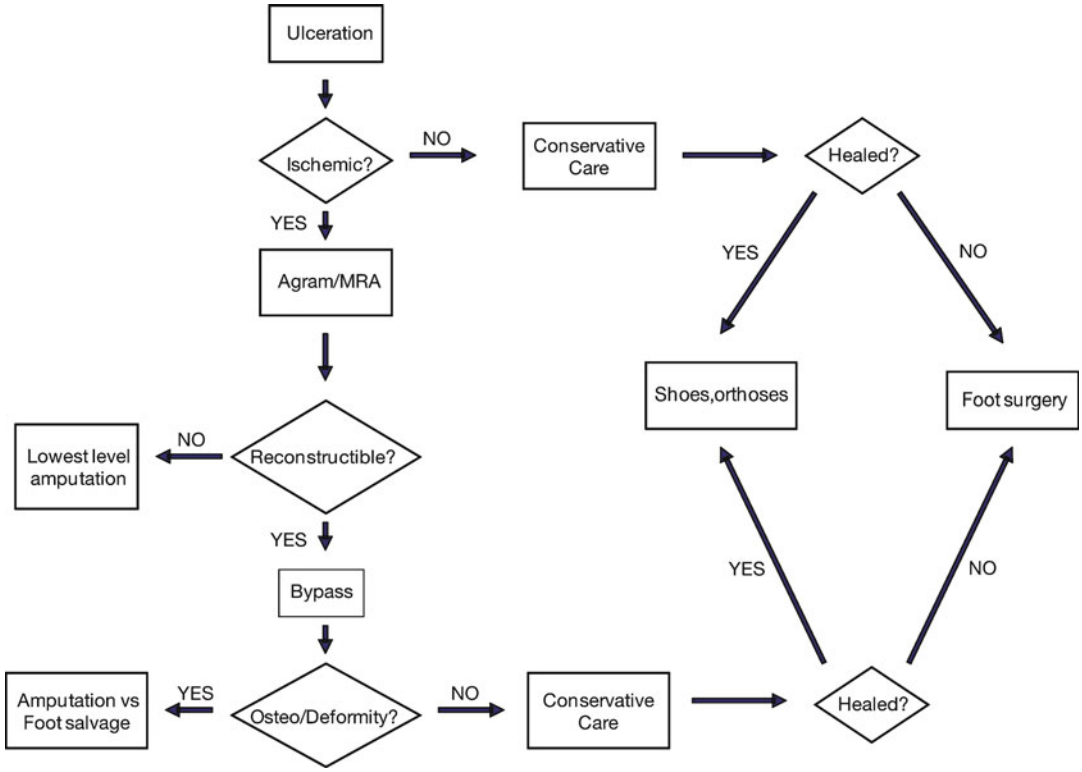

Fig. 23.2 Algorithm from the Joslin-Deaconess Diabetic Foot Center for the management of diabetic foot ulcers©

There must also be a recognized, systematic, and coordinated treatment plan. Patients will quickly pick up when physicians are at odds with each other when it comes to the treatment of their foot. These conflicts do not instill confidence in the patients of their treating physicians. "What should I do?" or "Who do I listen to" or "Who is right" are common questions that arise when mixed messages are given. Therefore, it is important that if there are disagreements or alternate treatment recommendations then these are resolved before presentation to the patient.

We have included an algorithm that represents our joint philosophy on the approach to diabetic foot problems (Fig. 23.2). This algorithm has been developed over the past 25 years from the joint experiences of the vascular surgeons and podiatrists of the Joslin-Deaconess Foot Center. By following this algorithm, we provide a systematic approach in the management of the majority of foot problems that we see. Also, because this algorithm was created jointly, there are few disagreements or deviations in the care of these patients. Once again, patients are very astute at recognizing when their treating physicians are in agreement on the care of their foot problem.

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Quality of Health Care

24

Emily A. Cook and Marcia A. Testa

Abstract

The challenge to deliver the highest quality health care to patients with diabetes is complex and multifaceted. The goal of this chapter is to provide the reader with a working knowledge of the conceptual framework of health care quality and measurement as applied in the treatment and management of diabetic foot care. A general understanding of the existing systems that monitor diabetes-related quality indicators and outcomes is summarized. Finally, additional information is provided on the current emphasis placed on the promotion of preventive services, reduction of quality gaps, and advancement of scientific knowledge through comparative effectiveness research.

Keywords

Heath care quality • Diabetes • Comparative effectiveness research • Quality indicators • Foot ulcers • Amputations

Defining "Quality Health Care"

> Quality health care means doing the right thing at the right time in the right way for the right person and having the best results possible
>
> Agency for Healthcare Research and Quality [1]

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Although this definition of "quality health care" emphasizes that superior health outcomes are the product of superior health care processes, scientific evidence supporting whether physicians are providing the right treatment at the right time in the right patient is extremely difficult to obtain. While most medical procedures and treatments have been shown to be efficacious, studies demonstrating the differential comparative effectiveness among efficacious treatments and interventions that could be used to optimize the quality of health care are relatively rare. The goal of this chapter is not to recommend the most effective treatments for diabetes and diabetic foot care that define high quality, but rather to provide the

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reader with a working knowledge of the conceptual framework of health care quality and measurement as applied in the treatment and management of diabetes foot care.

In addition to striving to ensure high quality in the delivery of health care services, physicians, health care managers, and administrators are equally concerned with the associated costs and resources that must be expended to achieve high-quality performance standards. As the demographic balance shifts in the USA to an ever-increasing aging population that consumes a larger proportion of the health care resources and as the US Government promises to expand health care to approximately 32 million Americans who are currently uninsured, issues relating to health economics and the cost-effectiveness of medical care interventions and programs have become even more important to the general population, legislators, and government officials. To ensure that all stakeholders communicate effectively about the quality of health care, it is critical that common terminology is used. This seems like a relatively simple requirement, but in fact it is quite challenging to decide upon a common nomenclature that is equally understandable and interpretable to patients, physicians, health plan administrators, politicians, legislators, and government officials. Physicians have a particularly critical role in these communications since they must effectively relate problems and concerns about the current and future state of health care between their patients and most other stakeholders.

In 2001, the Institute of Medicine published a consensus report, which described six performance goals for high-quality health care, namely, that, "… quality health care is safe, effective, patient-centered, timely, efficient, and equitable" [2]. Applying these descriptors as high benchmarks for assessing quality in the care of persons with diabetes is complicated by the fact that quantifiable metrics and standards for each must first be established. However, experts disagree about many definitions and fundamentals ranging from disease terminology to treatment plans, making consensus even more difficult. For example, some experts argue that the current health care system is "unsafe" and advocate massive system changes to reduce medical errors. One statistic that fuels these claims is the Institute of Medicine report in the year 2000 that between 44,000 and 98,000 hospitalized Americans died due to medical errors [3], making medical errors nearly as common as diabetes as a primary cause of death. Primary cause of death due to diabetes in 2000 was estimated to be 69,301, the sixth leading cause in the USA [4], although still less than the 213,062 deaths for which diabetes was listed as a contributing cause. A fairer comparison is that medical errors more than likely contributed to the majority of deaths rather than being a primary cause of death. Regardless, such large numbers of deaths due to medical errors raise concerns about quality since death is the worst possible outcome of such errors. Such statistics prove perplexing to the general public given that Americans spend more on health care than any other industrialized country, with future projections estimating that health care spending will exceed 20% of the US gross domestic product (GDP) by 2016 [5].

The current US health care system is largely reactionary, and shortcomings are frequently addressed in terms of improving the delivery of medical care. However, a broader framework should be embraced: one that recognizes that direct medical care is only one determinant of population health outcomes. In order to truly prevent, improve, and provide for the ever-expanding diabetes population, future policies must also utilize health models that incorporate nonmedical health determinants. One such model proposes that the health of a population can be determined through five primary domains: behavioral choices, social circumstances, environmental conditions, genetics, and medical care. To emphasize the relative importance of these domains, consider that it is estimated that 40% of preventable deaths are due to patient behavioral choices, such as poor diet, low levels of physical activity, and substance abuse, while only 10–15% are associated with errors in medical care. In addition, over 95% of health care dollars in the USA are spent on medical care with less than 5% spent on prevention and population-level health programs [6–8]. It is apparent that improving access to and the quality of medical care without simultaneously improving the four other health determinants will have a

Table 24.1 Foundation to measuring health care quality

Quality measure	Examples	Advantages	Disadvantages
Structure	– Hospital, clinic facilities – Proper equipment, operating room facilities, and efficiency – Proper training of physicians, nurses, etc. – Adequate administrative staff	– Usually, easy to gather data – Data is often objective (i.e., billing codes, administrative information)	– May be difficult to determine the extent of the relationship between the structure measurement and process and outcome measurements
Process	– Complete and timely screening examinations, exam skills – Proper referrals and use of multidisciplinary teams – Surgical technique – Proper choice of diagnostic tests and treatment choices	– May answer more relevant questions – Provides timely results for decision making	– May not relate to outcomes (improved process may not result in improved outcome)
Outcome	– Survival – Amputation – Success rates of surgical procedures	– Often easier to interpret – Often considered a more valid measurement – Often, objective measurements are available	– Choice of outcome may be immaterial (treatment may decrease amputation rates but may also decrease functionality and patients' quality of life) – May not be feasible or possible to determine causes of long-term outcomes, such as amputations – May not be possible to compare or produce timely results when decisions must be made – Certain outcomes are less objective or not applicable to certain patient populations (i.e., patient satisfaction, classifying outcomes as good or poor, instruments such as AOFAS scores, etc.)

relatively small impact on the overall population health. It is evident that methods used to evaluate health care quality in order to improve population health must take into account the multidimensional nature of health determinants.

How Do We Evaluate Health Care Quality in Diabetes?

In 1966, Avedis Donabedian, MD, MPH, published a seminal paper proposing effective methods for evaluating the quality of health care [9]. He proposed that health care quality could be assessed through three primary measurement domains, namely: structure, process, and outcomes. Structure measurements focus on the environment and support, where health care services are provided, such as hospital buildings, equipment, and staff. Process measures include the actual steps needed to carry out the health care services of interest, such as physical examinations, laboratory testing, surgery, and pharmacologic therapies. The last domain, outcomes measures, focuses on the end result of the health care services delivered, including laboratory results, levels of physical and cognitive functioning, quality of life, morbidity, and mortality. Each of these quality measures has positive and negative attributes with regard to our ability to measure and utilize them for quality improvement, but if applied concurrently, an even more accurate evaluation can be made (Table 24.1) [9].

The framework of evaluation can heavily influence perceptions of achievement and failure in health care quality. This is also true for specific disease management programs, including diabetes-related care. Stakeholders representing a wide range of values and perceptions often classify quality of care in diverse terms. For example, while an endocrinologist might identify patient medication compliance as an important indicator of health care quality, an insurer might place a greater emphasis on the length of a hospital stay for uncontrolled diabetes. Furthermore, the patient might view high health care quality as lengthening life or improving quality of life, while a public health official might focus on whether or not educational campaigns are able to prevent hospitalizations. These varying frameworks and perspectives make the measurement and evaluation of health care quality difficult to standardize.

The foundation of the surgeon's perspective of health care quality is largely attributed to the work of Donabedian and two surgeons, Ernest Amory Codman M.D. and Shukri Khuri M.D., M.Sc. Codman contributed by creating the "End Result Idea," where hospitals analyze treatment outcomes in order to improve health care quality. He also established the concept of morbidity and mortality conferences (established at Massachusetts General Hospital, Cambridge, MA), which has been widely adopted. Using this end results approach, all surgical cases are reviewed and complications assigned a root cause of either patient and/or surgical selection, surgeon technique and/or instrumentation, pre- or postoperative patient management, or patient comorbidities. Codman's innovation in quality monitoring contributed to his appointment as Chair of the Committee for the Standardization of Hospitals, now known as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). JCAHO was established in order to standardize minimum quality health care provided by the US hospitals. In 1996, JCAHO began recognizing health care organizations that utilize process and outcome measures for quality improvement through the development of the Codman Award [10, 11]. Khuri is well known for leading the development of a Department of Veterans Affairs prospective surgical surveillance system. This system was expanded into the National Surgical Quality Improvement Program (NSQIP), which is used to improve surgical morbidity and mortality throughout the USA [10]. In the context of diabetic foot management, a shortcoming of NSQIP is that its scope is limited to general and vascular surgery and has no direct reference to podiatric surgery. Given the ubiquity of diabetes, a nationwide surveillance system has the potential to enhance quality of care.

Quality of Care in Diabetic Limb Management

In order to understand the current quality of health care provided for patients with diabetes, a general understanding of the existing systems that monitor diabetes-related quality indicators (QIs) and outcomes is necessary. These systems include federal, state, and regional governments and public health levels, corporate and health insurance levels, specialized organizations and institutions, and even small groups and individuals. A brief review of these systems is given below.

The Department of Health and Human Services (HHS) in the USA, which operates under the executive branch of the government, is the primary agency charged with protecting Americans' health. The organization achieves this through the Office of the Secretary of HHS and its 12 agencies, with a workforce of over 65,000 employees and a total budget of approximately $700 billion [12]. Within this system, several agencies and centers comprise the monitoring and regulatory arms of health care quality as delineated below.

- Agency for Healthcare Research and Quality (AHRQ) studies utilization and cost of health care services, develops and studies quality measures, disseminates health outcomes research to improve health care quality, and supports evidence-based medicine.
- Centers for Disease Control and Prevention (CDC) prevents and controls disease both

nationally, through departments of public health, and internationally; it also surveys patient safety and health care quality.
- Centers for Medicare and Medicaid Services (CMS) provides health care coverage to older, disabled, and low-income Americans comprising 25% of the US population.
- Food and Drug Administration (FDA) is responsible for ensuring the safety and effectiveness of vaccines, medications, and other biologic products, products that emit radiation, medical devices, and food.
- Indian Health Service (IHS) improves chronic disease management and health care access, supports medical homes, and provides preventive and public health services to American Indians and Alaska Natives.
- National Institutes of Health (NIH) is the primary federal research agency and has the largest source of medical research funding worldwide.

The AHRQ's Healthcare Cost and Utilization Project (HCUP) provides states and organizations numerous public access databases and software tools to enhance their health care quality improvement projects. The HCUP databases bring together the data collection efforts of State data organizations, hospital associations, private data organizations, and the Federal Government to create a national information resource of patient-level health care data. HCUP includes the largest collection of longitudinal hospital care data in the USA, with all-payer, encounter-level information beginning in 1988. The HCUP QIs initially included 33 QIs that encompassed three dimensions of health care: adverse hospital outcomes, inappropriate use of hospital procedures, and preventing hospitalization for certain avoidable conditions. Several limitations were identified in the original HCUP databases. For example, the databases did not allow for risk or severity of disease adjustment. They utilized the actual number of hospital discharges rather than employing the population at risk in the denominator of rate calculations, and they focused more on surgically related outcomes rather than chronic diseases. In fact, the original HCUP data included only 2 of 33 QIs related to diabetes, namely, diabetes short-term and long-term complications (within the third dimension—avoidable hospital admissions) [13].

AHRQ has since revamped the HCUP QIs to now give greater emphasis to chronic diseases. The newer QIs measure multiple health care dimensions that allow policy makers, stakeholders, researchers, and physicians to identify quality gaps and track health care quality over time. The QIs are divided into four modules: prevention quality indicators (PQIs), inpatient quality indicators, patient safety indicators, and pediatric quality indicators. Software and user guides for all four modules are available to assist users in applying the QIs to their own data. These QIs still analyze available inpatient hospital discharge data. However, they also extrapolate those results to identify ways to improve the quality of preventive and outpatient care for a variety of health care conditions, including ambulatory care-sensitive conditions or ACSCs. There are a total of 14 ACSCs, and 4 ACSCs related specifically to diabetes: (1) diabetes short-term complication admission rate; (2) diabetes long-term complication admission rate; (3) uncontrolled diabetes admission rate; and (4) rate of lower extremity amputation (LEA) among patients with diabetes [13].

AHRQ measures diabetes-related process using the Medical Expenditure Panel Survey, Household Component (MEPS-HC). Analysis of this survey data found that only one-third of diabetic adults in the USA reported receiving three recommended services within the last year: a hemoglobin A1c test (HbA1c), a dilated eye exam, and a foot exam [14]. AHRQ has also produced two major reports that incorporate MEPS-HC information along with HCUP/AHRQ QIs: National Healthcare Quality Report (NHQR) and the National Healthcare Disparities Report (NHDR). The NHQR uses both process and outcome measures to assess and evaluate the quality of diabetes care in the USA. Process measures include whether an HbA1c test, retinal eye exam, influenza immunization, and foot examination were performed in the last year, while outcome measures include actual test results (HbA1c > 9.5% is poor, <9% needs improvement, <7% is good; total cholesterol <200 mg/dl is good; percent

with blood pressure <140/90 mm/Hg) and classification of "avoidable" hospitalizations. Here, hospitalization is an indicator of the health outcome "worsening physical health status" and avoidable hospitalizations have been defined as persons with diabetes admitted with uncontrolled diabetes without complications (absence of short- or long-term complications or LEA). Short-term complications are defined to include ketoacidosis, hyperosmolarity, and coma. Long-term complications include renal, eye, neurologic, circulatory, or other unspecified diagnosis related to diabetes. LEAs are estimated by the CDC through a representative national sample (~500 hospitals, 270,000 records) of administrative hospital discharge records and inpatient reimbursement claims called the National Hospital Discharge Survey (NHDS) [15]. Health care quality estimates from the NQHR and AHRQ are summarized in Tables 24.2 and 24.3.

A composite measure of diabetes care effectiveness comprising three criteria has been used to identify gaps in quality. In the NHDR, it was reported that Hispanics aged 40 and older, with no more than a high school-equivalent education level and financially classified as poor, near-poor, or middle-income people, were significantly less likely than others to receive all three recommended diabetes services (HbA1c, dilated eye exam, and foot exam). Another recognized disparity relates to diabetes-related LEAs, where Black-non-Hispanic males had a higher incidence than White-non-Hispanic males and Black-non Hispanic females [15].

The CDC, with assistance from states, oversees the behavioral risk factor surveillance system (BRFSS). The BRFSS is a telephone health survey that tracks diseases and risk behaviors in the USA by calling citizens at random. In regard to lower extremity, the BRFSS surveys two process measures as part of an optional state module on diabetes: self-foot exams and foot exams by health professionals. This diabetes module was used by an average of 41 states between 2005 and 2009. Although they differ in survey methods and definitions, there are some similarities to MEPS-HC. An important distinction is that BRFSS results can be compared between states if the module is used. The BRFSS is one of the only tools with which states have to obtain reasonably current information in order to track lower extremity quality process measures. The CDC also provides reports, such as the Morbidity and Mortality Weekly Reports, charts, graphs, and searchable databases for interested parties to compare and analyze results in a timely fashion. The results of this survey have provided data showing that the rates of foot exams performed by health professionals over the last 8 years nationally have improved from just over 60% to just under 70% (nearly 20% of the goal). However, rates of self-foot exams did not improve substantially during that same period (Figs. 24.1 and 24.2). These findings further support the belief that the greatest improvements in population health require more attention to be paid to patient behavior.

There are some well-known limitations in the BRFSS approach. One limitation is that the survey might miss some of the highest risk groups (those without residential telephones, institutionalized patients, unable to speak English or Spanish). Another limitation is that it relies on patient recall and perceptions, and utilizes smaller survey sample sizes in order to reduce costs of administering the surveys. Moreover, additional data and analysis are needed to determine the reliability and validity of this self-reported BRFSS and MEPS foot exam measures [16].

The CDC also administers the National Health and Nutrition Examination Survey (NHANES) through the National Center for Health Statistics (HCHS). NHANES includes data from a combination of patient interviews, physical examinations by physicians, and laboratory results with the extent of data obtained dependent upon the disease and condition of the patient. Diabetes-related data include BRFSS survey questions; laboratory results, such as fasting glucose, insulin, glycohemoglobin, and oral glucose tolerance test; lipid panel; renal function; and physical examination results, including weight, height, and blood pressure. The primary advantage of NHANES as compared to patient surveys is that it includes outcome data on actual laboratory and physical examination results. Disadvantages include that it is time intensive

Table 24.2 Quality measure estimates of adults with diabetes with respective benchmarks

Quality measure[a]	Source[a]	Result[a]	Theoretic goal[a] (%)	Best-in-class goal[a]	National consensus goal[a]	Regional average goal[a]			
						Northeast	Midwest	South	West
HbA1c test in last year, %	BRFSS (2000)	59% (SE 1.0)	100	95.6%	65%	85.5%	85.2%	80.2%	83.2%
Retinal eye exam in last year, %	BRFSS (2008)	62.2% (SE 1.0)	100	79.6%	76%	71.1%	72.5%	65.2%	63.4%
Foot exam in last year, %	BRFSS (2008)	67.2% (SE 1.1)	100	81.3%	91%	68.6%	68.9%	63.9%	67.9%
Influenza immunization in past year, %	BRFSS	49.6% (SE 0.8)	100	59.0%	60 or 90%[a]	42.6%	46.1%	39.2%	40.7%
Hospital admission for uncontrolled diabetes per 100,000 population	HCUP/QIs (2006)	21.6 (SE 1.1)	0	3.75	54 (HCUP 1996)	30.1	28.0	35.7	15.6
Hospital admission for short-term complications per 100,000 population	HCUP/QIs (2006)	31.8 (SE 2.8)	0	16.45	N/A	48.1	45.4	61.4	43.3
Hospital admission for long-term complications per 100,000 population	HCUP/QIs (2006)	126.9 (SE 3.6)	0	68.48	N/A	135.8	109.7	133.6	96.2
Hospital admissions for diabetes-related nontraumatic LEAs per 1,000 persons with diabetes	NHDS (1998–2000)	4.8 (SE 0.4)	0	N/A	2.9	N/A	N/A	N/A	N/A

Table created from data in references 13, 15, 16, 22, 107 (*SE* standard error)

[a]Information relating to the regional averages is from the National Healthcare Quality Report, AHRQ, 2003. Not all states participate in BRFSS and HCUP/QI measures. Some data fluctuates and/or is from a small sample size requiring averaging across several years to improve estimates. The national consensus is the Healthy People 2010 report which compares BRFSS and NHDS data. Healthy People 2010 does include influenza immunization but does not specify for people with diabetes. Goals are to achieve 90% influenza immunization in noninstitutionalized adults aged 65 and older and institutionalized adults aged 18 and older and 60% influenza immunization in noninstitutionalized high-risk adults aged 18–64 years. Best-in-class benchmarks were calculated by averaging the top 10% of participating states for a given quality measure

Table 24.3 Quality measure estimates from MEPS and NHANES with directed benchmarks

Quality measure[a]	Source[a]	Results[a]	Best-in-class average[a] (%)	Possible states targeted for improvement[a]
HbA1c test in last year	MEPS (2006)	89.6% (SE 1.0)	91.5	Arkansas, Connecticut, District of Columbia, Louisiana, Nevada
HbA1c <7%	NHANES (1999–2000); MEPS (2003–2006)	37% (SE 3.8) 54.6% (SE 2.8)	N/A	N/A
Lipid profile in last 2 years	MEPS (2000)	94.32% (SE 0.87)	N/A	N/A
Total cholesterol <200 mg/dl	MEPS (2003–2006)	54.9% (SE 2.4)	N/A	N/A
Blood pressures <140/90 mmHg	NHANES (1999–2000); MEPS (2003–2006)	59.3% (SE 3.5) 58.5 (SE 2.5)	N/A	N/A
Dilated eye exam in last year	MEPS (2006)	59.3% (SE 1.5)	76.05	Alabama, Arkansas, Kentucky, Idaho, Nevada
Foot exam in last year	MEPS (2007)	69.1% (SE 1.6)	81.15	Arizona, Arkansas, California, Kentucky, Nevada
Influenza immunization in past year	MEPS (2007)	59.1% (SE 1.6)	66.26	Florida, Kansas, Mississippi, Oregon, Texas

Table created from data in references 13, 15, 17 (*SE* standard error)

[a]MEPS data cannot be compared to BRFSS data due to large differences in survey methods, definitions, populations, etc. For example, BRFSS uses populations between the ages of 18–64 while MEPS utilized adults over 40 years old. There are also differences in methods of adjustment. Some data fluctuates and/or is from a small sample size requiring averaging across several years to improve estimates. Not all measures have data reliable enough to report state-level comparisons. Not all states participate in MEPS. Possible states targeted for improvement measures were defined as the bottom five states according to a given MEPS quality measure for that year. This may not reflect the bottom five states as process measures usually do not affect outcome measures within the same time period. Best-in-class benchmarks were calculated by averaging the top 10% of participating states for a given quality measure

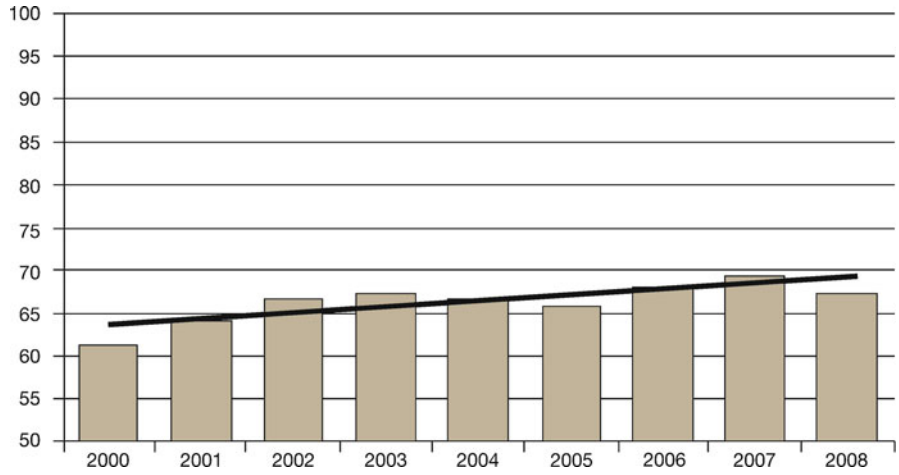

Fig. 24.1 Percent of adults with diabetes receiving a foot examination within the last year, as per BRFSS data with trend line, 2000–2008, age adjusted [16]

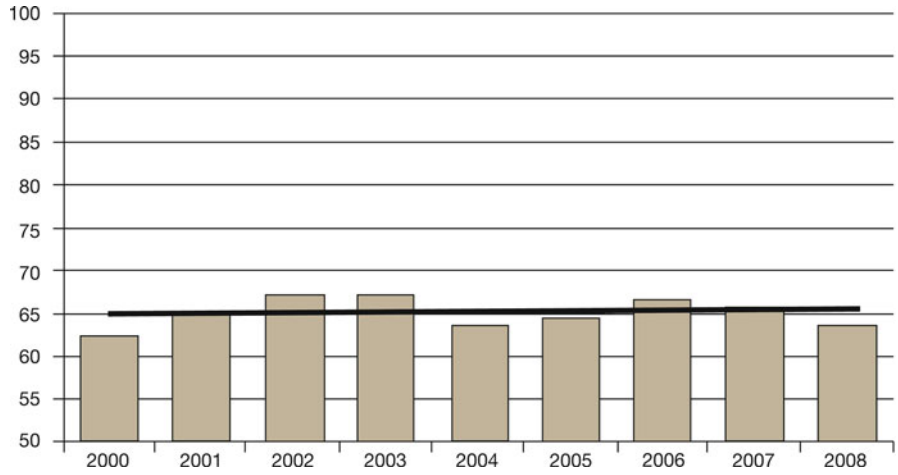

Fig. 24.2 Percent of adults with diabetes performing daily self-foot exams as per BRFSS data with trend line, 2000–2008, age adjusted [16]

and cost prohibitive, and as such, samples sizes are relatively small. State-level data is also not available and comparisons must be made to national benchmarks [17].

Each year, the HHS promotes a healthy people agenda (e.g., Healthy People 2010), which provides a framework for prevention for the health of the US population. The yearly reports promote target national health objectives designed to identify the most significant preventable threats to health and to establish national goals to reduce these threats. Using data from the CDC's survey, the Healthy People 2010 report details several health objectives for the nation specifically related to lower extremity problems from diabetes [18].

- Reduce the rate of LEAs in persons with diabetes from a baseline of 6.6 LEAs per 1,000 people with diabetes (1997–1999 rate age adjusted to the year 2000 standard population) to a target of 2.9/1,000. The data sources listed are the NHDS and the National Health Interview Survey (NHIS), from the CDC's HCHS.
- Increase the proportion of adults with diabetes who have at least an annual foot examination, from a baseline of 68% in 1998 (age adjusted to the year standard 2000 population) to 91%. The data source is the BRFSS, conducted by the CDC's National Center for Chronic Disease Prevention and Health Promotion.

Reduction in the frequency of foot ulcers was originally included as a performance objective in Healthy People 2010 but was deleted because it was determined during the midcourse review that NHANES data on this topic was unreliable. This points to the fact that even within NHANES, adequate quality performance data collection and measurement are difficult. Other relevant objectives in Healthy People 2010 include improving the prevention and diagnosis of diabetes and increasing the proportion of people with diabetes who perform self-monitoring of blood glucose at least once daily. Table 24.2 includes the Healthy People 2010 goals for each available QI [18].

Controversy and differences of opinions exist regarding benchmarks for quality improvement in diabetes. There are several approaches for selecting quality standards and benchmarks. Most quality metrics are recommended by professional organizations. One major diabetes professional organization, American Diabetes Association (ADA), publishes its standards each year regarding high-quality care standards [19]. The section on "Foot Care" emphasizes the importance of an annual foot examination to identify foot ulcers and the screening of individuals at higher risk for ulcers and amputation, including those with previous amputation, ulcer history, peripheral neuropathy, foot deformity, peripheral vascular disease, visual impairment,

diabetic nephropathy, poor glycemic control, and history of cigarette smoking [19]. The American Association of Clinical Endocrinologists (AACE) also provides clinical practice guidelines for diabetes mellitus treatment. The AACE also supports annual comprehensive foot examinations, which include assessing for neuropathy and mechanical foot changes. Patients should be referred to a podiatric surgeon, vascular surgeon, orthopedist, and/or neurologist depending on the risk factor(s) identified [20, 21].

While it may be easy to identify optimal outcomes associated with best care processes based on theoretic benchmarks (i.e., no amputations, 100% foot exams), practical restrictions limit their use. A well-documented limitation is that the use of national or state averages as benchmarks is not adequate for advancing quality improvement across a wide spectrum of local diversity. Averages fail to take into account severity adjustments for areas with high-risk populations. Because of these factors, national and state averages have generally been reserved for tracking and surveillance rather than for comparative benchmarking, which requires adjustment for potential confounders. Two benchmarks currently in vogue are national consensus goals and best-in-class goals. An example of the former benchmark is Healthy People 2010, whereby the CDC reports national consensus goals. There are different methods in which best-in-class benchmarks are calculated. The method of calculation determines the utility of this point of reference. It is also important that comparisons are made with similar sources and definitions [22]. Tables 24.2 and 24.3 include several benchmarks for comparison of diabetes-related QIs.

The National Committee for Quality Assurance (NCQA) is responsible for accrediting health plans. CMS also requires health plans to report using the Health Plan Employer Data and Information Set (HEDIS). HEDIS measures are designed to allow comparisons between health care systems, although measures are also used to assess for health care quality improvement in a variety of ever-expanding ways. The majority of health insurance plans utilize the HEDIS produced by a national, nonprofit organization, the NCQA. HEDIS measures are published in their database as well as an annual report: The State of Health Care Quality. The information is used by health insurance companies, CMS, researchers, and other consumers to compare health care quality at several levels. For example, national magazines and media have published "America's best health plans" based on this data. Although controversial in its methods, comparisons may be made between physicians, otherwise known as physician profiling, and data can be reported by physician level [23].

HEDIS quality measures are multidimensional, rigorously developed, and defined with importance placed on the measure's relevance, scientific soundness, and feasibility. Each measure is periodically updated (i.e., revised in order to stay current in today's health care environment). They are organized into 8 domains with a total of 74 either single or composite measures as follows—domain (number of measures in 2010/2011): effectiveness of care (37/40), access/availability of care (7/7), satisfaction with the experience of care (3/3), use of services (13/12), cost of care (7/7), health plan descriptive information (6/6), health plan stability (1/1), and informed health choices (currently, no measures in this domain). Comprehensive diabetes care is among the most frequently monitored health issue that HEDIS measures. Physicians are contractually obligated to provide medical record information in a timely fashion when requested by health plans for HEDIS measures [23]. To provide clinicians with tools to support the delivery and recognition of consistent high-quality care, NCQA in partnership with the ADA developed the Diabetes Recognition Program (DRP). This voluntary program is designed to recognize physicians and other clinicians who use evidence-based measures and provide excellent care to their patients with diabetes. The data is analyzed, for a fee, to determine if evidence-based medicine and "excellent care" are provided, based on 10 measures from 25 patient charts. Patients and other consumers may publically identify those physicians recognized by NCQA for providing consistent high-quality care in diabetes based on this process. There are also incentive programs encouraging eligible physicians to report data on

Medicare beneficiaries (known as the Physician Quality Reporting Initiative through CMS) [24]. Bridges to Excellence, advocated by Berwick and the IOM report, Crossing the Quality Chasm, further promotes the pay-for-performance model to improve the quality of care delivered by utilizing a cash bonus system for physicians in the Diabetes Physician Recognition Program [24, 25].

Diabetes Quality Improvement Initiatives

In addition to the DRP described in the previous section, there have been a plethora of other diabetes quality improvement programs originating from diverse sources. One substantial project is the Diabetes Quality Improvement Project (DQIP), which consists of an alliance of both private and public groups, such as the ADA, CMS, NCQA, JCAHO, American Medical Association, and Department of Veterans Affairs. The chief contribution of this collaboration was the development of unanimously supported national health care quality measures that evaluated diabetes care. These standardized measures are published through the "Report Card" using a variety of data resources, including BRFSS and NHANES. As with most quality measures, whether or not a foot examination was performed is included as one of the primary QIs [26].

Since conventional health care systems in the USA are designed to provide symptom-driven responses to acute illnesses (i.e., reactionary medicine), they are poorly configured to meet the needs of the chronically ill [27]. As such, the Chronic Care Model is a quality improvement concept that has gained popularity for patients with chronic disease, including diabetes. The underlying principle of the Chronic Care Model as applied to diabetes is that all aspects of diabetes care are provided in a multidisciplinary setting that emphasizes proactive prevention screening practices over reactionary medicine. In the Chronic Care Model, the system is altered to globally address diabetes by improving the community, physicians, and facilities which provide care. The Chronic Care Model can be applied to the care of the diabetic foot by including the following essential core elements [28, 29]:

- *Organization of Care*: Preventing ulcers and amputations as an organizational priority with leadership support; establishing defined targets, evidence-based policies, and incentives to increase screening
- *Clinical Information Systems*: Establishing registries and, if available, using electronic medical records to track patients by risk strata, giving clinicians performance feedback and risk-level-appropriate reminders for patients and providers; extracting and summarizing data from previous encounters to facilitate good clinical decision making
- *Delivery System Design*: Providing planned visits and other proactive mechanisms for risk-stratified screening, clinical care, and follow-up in primary care; facilitating regular, meaningful coordination and interactions of foot care team members and primary care providers on the basis of stratified risk level
- *Decision Support*: Implementing evidence-based guidelines, specialist referral guidelines, and online tools; training of providers/teams; feedback and patients' progress reports
- *Self-Management Support*: Providing self-help instruction and materials to patients and families, linked to patient-identified priorities
- *Coordination of Community Resources*: Activating patients' participation in effective community programs

Independent not-for-profit organizations, such as the Institute for Healthcare Improvement (IHI), have contributed to substantial improvements in a variety of health care settings based on time-tested quality improvement tools. IHI advocates the Plan–Do–Study–Act (PDSA) model, where small tested steps in change lead to desirable improvements in health care structure, process, and outcome measures. A theoretical example is provided in Fig. 24.3, where IHI resources were used to build a quality improvement tracker [30, 31]. The PDSA is guided by three fundamental questions as follows.

1. What are we trying to accomplish? The aim must be measurable, within a specified population, and have a specific deadline.

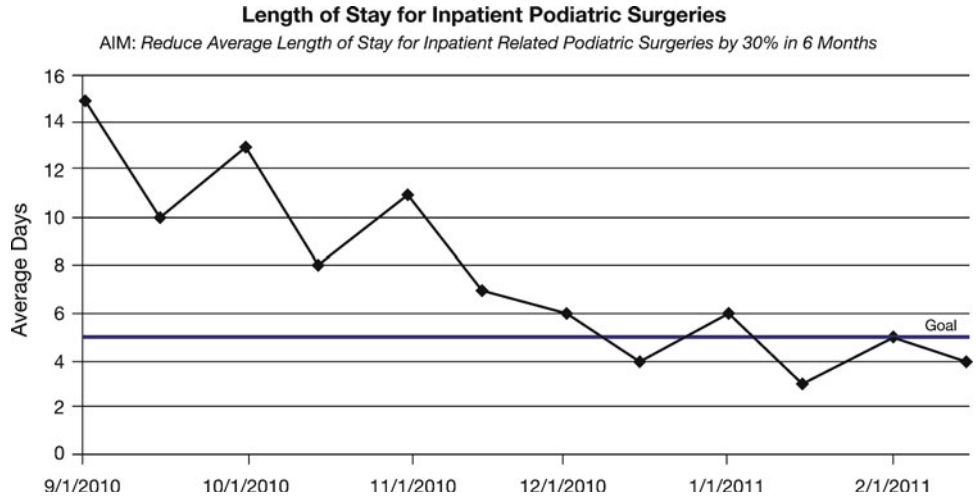

Fig. 24.3 Example of a method to track monthly quality measures for PDSA cycles [32]

2. How will we know that a change is an improvement? Quantitative measures are defined as a structure, process, or outcome measure.
3. What changes can we make that will result in improvement? Change does not always equate to improvement; changes are carefully selected.

The selected change is then put through rapid cycle testing, the PDSA model, which utilizes the information learned to guide future change (Fig. 24.3). This preliminary change may be discontinued, refined, or implemented on a larger scale or even an entire organization based on the results [32, 33].

Multiple PDSA cycles can be effectively utilized to drive meaningful change in all fields of health care, including diabetes. For example, the California Health Care Safety Net Institute in Oakland, CA, created a collaborative with aims to improve the quality of care given to diabetics in several public hospital clinics. These aims focused on improved glycemic control, reduction of cardiovascular risk factors, and improvement in patient self-management. Specific goals by a designated time frame were identified, as well as structure, process, and outcome measures. Meaningful changes were selected that were believed to achieve the aims and multiple PDSA cycles were implemented. Some of the selected changes included decision support changes (uniform use of diabetes clinical guidelines, integrated communication between primary care and specialists), self-management support, delivery system design changes (specialized medical assistant training, establishing referrals to podiatry, establishing risk stratification systems, culturally appropriate educational materials, etc.), and clinical information system changes (creation of diabetes disease registry, automated alerts for overdue exams and tests, provide feedback to physicians and patients). Within 7 months, measurable improvements were seen in patient self-management by almost 50% of the patient panels, including the proportion of foot examinations (from <20 to 60%), and overall reduction in average HbA1c and LDL cholesterol levels. The collaborative realized that without strong senior leadership most initiatives are unsuccessful, information technology is critical and requires more attention, and understaffed clinics with part-time staff can struggle and suffer compared to clinics with adequate staffing and greater continuity of care [34].

There are many other DQIPs both at the state and institutional levels. To improve the quality of diabetes care and outcomes and to disseminate health awareness through public relations and communication, many states have formed

diabetes task forces, initiated self-management and patient education programs, supported provider training programs, developed minority and rural outreach programs, implemented information technology systems, and established collaborations with health plans, community health centers, communities, and other agencies. State governments have recognized that in order to control Medicaid-related health care costs quality of care in diabetes must be addressed [22].

Effectiveness of Diabetes Quality Improvement Programs

The impact and level of effectiveness of the numerous quality improvement programs for diabetes are difficult to assess. Quality measures, such as LEAs, are long-term outcomes, and implementation of quality improvement programs cannot efficiently assess if reduction in amputations will occur in a timely manner. Instead, process measures, such as whether or not a foot examination was performed, are routinely monitored. The validity of the process measure is based upon the existence of a causal relation between improvement in the process and improvement in the outcome. It is assumed that by conducting a foot-screening examination risk factors leading to LEA are identified and then appropriately modified, and subsequent amputation rates are reduced. The ability of this process measure to predict outcome is subject to wide variation throughout the USA since the quality of the foot-screening exam, not just whether or not it has been done, is important to the validity of the causal relationship.

Some evidence suggests that annual office visits may often fail to include foot examinations [35]. In one managed care program, 94% of patient records failed to note that a foot examination had been conducted [36]. One example can be drawn from state-level monitoring and surveillance. For example, according to the Massachusetts Department of Public Health, BRFSS results for Massachusetts indicated that the overall percentage of people with diabetes who received preventive foot exams from 2003 to 2005 was 76.7% compared to 66.6% nationally [16, 37]. This number has increased from 67% in 1999, but remains far short of the Healthy People 2010 goal of exceeding 90% [18].

Even if a diabetic lower extremity screening examination is performed, the quality and components of the examination are often poorly defined and may not adequately identify risk factors. This is partially due to multiple foot examination guidelines in existence, including local [38], state [39], national [40–42], and international guidelines [43] and specialty group [42] and individual recommendations [44–47]. The foot exam can identify many risk factors; however, variations in the exam are large and little is known about the current lower extremity exam strategies for gatekeepers, such as general practitioners. Existing research further suggests that foot-screening examinations conducted by general practitioners are unlikely to reduce foot complications "unless they eventuate in appropriate specialist referrals" (i.e., podiatric and vascular surgeons) [48]. Appropriateness of referrals is also difficult to define, as risk factors identified may also drive the urgency to address an issue (e.g., foot ulcer, infection, Charcot neuroarthropathy, etc.).

The limited amount of time allotted to physical examinations is a significant problem for over half of the general practitioners [49]. Within an annual diabetes exam, primary care providers are expected to identify and address the key tests and exams, including HbA1c, blood pressure, lipid panels, microalbumin measurements, serum creatinine, weight, nutrition, physical activity, medication and insulin adjustments in some, cardiovascular risk factors, dilated eye exams, other nonrelated patient concerns and conditions, as well as a comprehensive foot examination. The mean duration for a diabetes exam has been estimated to be 17.4 min [50]; however, the average time required for a comprehensive lower limb screening is at least 30 min [51]. From 1997 to 2005, the number of medical problems a general practitioner addresses has significantly increased while examination time has decreased. This has resulted in less time available per problem regardless of age group, with substantial reduction in time per problem in patients ≥65 years [52].

By necessity, the comprehensive diabetic foot examination may be placed as a lower priority unless there are active known problems.

There are numerous other barriers that inhibit implementing the most effective prevention strategies in lower extremity complications related to diabetes. These include barriers related to patients, cultural characteristics, physician training, health plans, systems of care, societal factors, workplace, community, and the environment. Physicians in private or small group practices are unlikely to have access to the same support as those in multispecialty groups or institutions. In addition, a greater emphasis is traditionally placed on reactionary medicine (i.e., after a patient develops a foot ulcer) and more focus is needed in addressing reimbursement and health insurance coverage issues as well as physician and patient education for preventive diabetic foot-screening exams. Low levels of patient compliance and education are well-known barriers, but access to primary and specialist care is still more predictive of the probability of screening exams than patient-level factors [53, 54].

Finally, there are known disparities in the quality of lower extremity diabetes care. In the USA, LEAs from diabetes are more common among African–Americans than other groups, and have been estimated to occur almost twice as often among African–Americans than among Whites [55, 56]. Rates also have been found to be higher among men compared to women, as well as in non-Hispanic Whites as compared to Hispanics [57]. Data from the state of California provide support for these findings, with a 1991 incidence of diabetes LEAs among African–Americans of 9.5/1,000, compared to 5.6 among non-Hispanic Whites and 4.4 among Hispanics [58]. South Asians have one-quarter the risk of LEA of Europeans, a difference that has been attributed to lower rates of neuropathy and PAD [59]. Research also suggests that American Indians may be at a higher risk for amputation than other groups [60]. The Chronic Care Model may be useful in that health systems' changes, with a target in high-risk groups, can integrate a multidisciplinary team approach that leads to effective prevention strategies.

Comparative Effectiveness

Comparative effectiveness research (CER) has become quite popular in recent years, especially since the American Recovery and Reinvestment Act of 2009 was signed into law. This Act assigned $1.1 billion to promote CER development and dissemination in health care [61]. CER compares ways in which health care conditions are diagnosed, treated, monitored, and even prevented. CER goes beyond simply comparing treatment A to treatment B, although there is great interest in comparing different treatments for a given health condition. CER also includes studying the effects of changes in the health care delivery system, and behavioral interventions [62]. Quality of life should also be considered and, although difficult to measure, is important to consider when determining the true impact of a treatment on a patient [63–65]. A major limitation in assessing quality in the field of the diabetic limb is that the majority of treatments provided, especially from a surgical perspective, cannot undergo or have not undergone evaluation through placebo-controlled randomized trials. CER is even less common, making it difficult for physicians to determine treatment choices without developing a certain level of experience. Some researchers and physicians try to compare studies, either informally or through systematic reviews and meta-analyses, but small differences in the patient populations, inclusion and exclusion criteria, and methods in treatment make it difficult and sometimes impossible to draw valid comparative conclusions. Another controversial subject is whether or not cost should be included in a comparative analysis as this may impact the health insurance coverage of a treatment [62]. Finally, even if CER were able to identify an effective treatment, there will still be issues with overuse and underuse estimates. This is particularly true if estimates are based upon consensus guidelines instead of rigorous scientific evaluation of a treatment [66].

CER is needed to sort out the effects of numerous treatments for diabetic foot ulcers (DFUs). Most treatments are compared to a standard of

care with or without placebo. Standard wound care typically consists of sharp debridement, moist dressings, off-loading, addressing infection, and evaluating vascular status. The problem is that studies have shown that this standard of care usually results in only one-fourth of wounds healed after 12 weeks and up to one-third of wounds healed by 20 weeks [67]. Clearly, there must be other methods utilized in order to promote faster wound healing than this currently accepted "standard of care." From hyperbaric oxygen to tissue-engineered cell-based skin equivalents, little research exists comparing similar treatments. The major challenge is that such high-quality clinical trials would be prohibitively expensive to conduct as the anticipated effect difference between two products would be much smaller than each individual product compared to the standard of care. The sample size required to detect relatively small, but clinically meaningful, effects would drive cost and time up substantially [66, 68]. Since most CER utilizes systematic reviews, electronic patient records, registries, and other longitudinal databases, but not clinical trials, causality cannot always be fully established. There are several efforts underway to utilize electronic medical records to conduct quality assessment and reviews. In addition to the large patient electronic databases already in existence [69–75], the AHRQ has teamed with the American Academy of Family Physicians to establish a large linked, networked database specifically for collecting longitudinal data for CER. This database called the Distributed Ambulatory Research in Therapeutics Network (DARTNet) is a federated network of electronic health databases created in 2008. Its purpose is to facilitate quality improvement of primary health care and efficiently compile clinically enriched data for CER. A federated network, such as DARTNet, links geographically and organizationally separate databases to allow a single query to pull information from multiple databases while maintaining the privacy and confidentiality of each database [76].

Other treatments, such as surgical off-loading, may also be efficient and effective in healing and preventing the recurrence of DFUs. Podiatric surgeons who believe in surgical off-loading provide this type of treatment because of evidence provided by a few studies, experience, and successful personal results [77–80]. Therefore, CER and published data cannot be the only determining factor in treating DFUs.

CER must also consider that the primary prevention of foot ulcer and prevention of ulcer recurrence are both important considerations. The recurrence of a healed ulcer is a common event, particularly when the underlying causes, such as peripheral neuropathy, PAD, calluses, increased pressure, and foot deformities, are still present. Ulcer recurrence rates have been found to range from 28% at 12 months [81] to 100% at 40 months [82–84]. Residual scar tissue following ulcer healing is less durable and vulnerable to the pressures of walking [35]. Several studies suggest that the use of therapeutic shoes may be effective [82, 84, 85]. For example, a London study found that the reoccurrence of ulcers among patients wearing therapeutic shoes was 17%, compared to 83% among those who returned to wearing normal shoes [86]. However, guidelines for the prescription of footwear are not standardized and few practitioners measure pressure at previous ulcer sites to ensure that high pressures are reduced by the footwear [85]. Whether or not all patients identified as being at risk should be provided with custom footwear is still under debate [87].

Prophylactic surgical off-loading may also prevent ulcer recurrence. This type of surgery aims to reduce the risk of foot ulcers by correcting deformities [77–80]. It may be determined that the presence of bony deformities and structural malalignment is too great and that the increase of ulceration or recurrence is too high. Although prophylactic surgery may provide a great benefit, long-term studies and CER are needed to demonstrate its effectiveness and surgical indications.

Health care delivery systems and behavioral intervention studies primarily address prevention of lower extremity complications that would lead to the development of DFUs and LEAs from diabetes. Research conducted over the past 25 years suggests that the types of health care delivery systems most likely to be successful in preventing

foot ulcers and LEAs among people with diabetes are integrated multidisciplinary teams (i.e., podiatric surgeons, general practitioners, vascular surgeons, nurses, dieticians, endocrinologists, plastic surgeons, pedorthists, infectious disease specialists, ophthalmologists and optometrists, diabetes health educators, etc.) with risk-stratified interventions directed at patients, providers, and health care systems [29]. A retrospective cohort study of 485 diabetic patients found that those who received podiatric care had greater survival and lower incidence of new foot ulceration than those who were not treated by a podiatric limb preservation team [88]. As wound healing and prevention of foot problems are complex, the expertise of many disciplines may be needed [35]. The practical guidelines of the International Consensus state that LEA rates can be reduced by 49–85% through a multicomponent strategy that addresses prevention, staff and patient education, multidisciplinary treatment of foot ulcers, and close monitoring [43, 89]. A study of interdisciplinary preventive foot care at ten Veteran Affairs medical centers identified six specific items that were associated with a lower rate of LEAs [90]. They were the following: addressing all foot care needs; making appropriate referrals; having ease in recruiting staff; having confidence with staff; availability of stand-alone, specialized, diabetic foot care services; and having providers who attended diabetic foot care education in the past 3 years. Together, these six items had a negative correlation coefficient of $r = -0.3$ with major amputations.

A prospective 5-year study examined the effects of implementing the International Consensus recommendations in Pistoia (Tuscany, Italy), where all DFUs are seen by a multidisciplinary care team [91]. The study found that after implementation of the International Consensus [89] both the number and duration of hospitalizations decreased. The study identified a reduction in major amputations and a relative increase in minor amputations. Among the aspects of the program that were deemed particularly effective were its focus on the early detection of ulcers by general practitioners, a foot care education program for patients, simple and rapid admission of patients to the hospital foot clinic, and qualified treatment by the specialist foot care team.

Patient self-management is particularly important for managing diabetes and preventing complications. Studies have demonstrated that patient self-management programs are effective tools for improving patient outcomes. One Stanford University study funded by AHRQ found that over a 2-year period participants in a chronic disease self-management program showed reductions in health distress, made fewer visits to the doctor's office and emergency room, had not experienced any further increases in disability, and had increased self-efficacy [92]. Systematic reviews of the literature on self-management programs for diabetes found positive effects on patients' knowledge, self-monitoring of blood glucose, diet, and glycemic control [93, 94]. Patient compliance is another important factor when assessing the feasibility of quality improvement programs. In one study, use of an integrated multidisciplinary team was found to lead to a low incidence of LEAs (1.1 per 1,000 persons per year). However, patient adherence was a key issue. Among high-risk persons, those who missed more than 50% of their appointments with the team were 54 times more likely to develop an ulcer and 20 times more likely to require an amputation than those who kept most appointments [95]. CER must also include patient behavior in order to achieve its full benefit. Although patient education in foot care and foot inspection has been described as the most important factor in preventing amputation [35], relatively little research has been performed on this topic, and most studies have had a short follow-up period. Most existing studies have emphasized foot care and measured changes in behavior and cognition, rather than ulcer and amputation prevention [48]. Some studies suggest that patient education improves short-term knowledge and may modestly reduce the risk of foot ulcers and amputations [96–98]. However, one study noted that the methodological quality of the nine available randomized controlled trials was poor. The review found weak evidence that patient education might reduce foot ulcers and amputations, especially among high-risk patients [98].

Research is also lacking regarding the most effective content of patient education. As noted in the International Consensus [43], the goal of patient education should be to increase motivation and skills and enhance recognition of potential foot problems and taking of appropriate action. Education should be provided over multiple sessions and using a combination of methods. In its recommendations regarding patient education, the ADA notes that patients at risk should understand the implications of the loss of protective sensation, the importance of monitoring their feet on a daily basis, the proper care of the foot, and how to select appropriate footwear [99]. Some publications support using clinical tools for enhancing patient self-monitoring. As described by Lavery et al., the incorporation of a handheld infrared skin thermometer into patients' self-care routine was found to be effective in preventing foot complications among at-risk individuals [100, 101]. The authors note that, with the exception of traumatic wounds, areas that are likely to ulcerate often have increased temperatures due to inflammation and autolysis of tissue. Using this tool, patients assigned to the enhanced therapy group measured the temperature on the sole of the foot in the morning and evening. When elevated temperatures were found, patients were instructed to reduce their level of activity and contact a study nurse. The enhanced therapy group was found to have significantly fewer diabetic foot complications than the standard therapy patients [100, 101].

CER is also needed to address the most effective interventions for physician education. The ADA recommends that all practitioners serving people with diabetes be able to perform a simple screening exam [99]. Therefore, physicians may benefit from training on best practices regarding the performance of the annual foot exam. An intervention addressing physician education is Project LEA prevention (LEAP), developed by the US Department of HHS, which offers a 1-day workshop on diabetic foot care. The project has been found to improve the rate of documenting foot care education, increase self-management, and to be associated with a trend towards reduced LEAs [102]. Another type of strategy targeting physicians has been the use of a computerized registry to remind physicians to enter the patient's risk status for LEA [103]. An additional approach is to implement clinical practice guidelines for foot care. As noted earlier, several guidelines have been published in the USA and abroad, including the Practical Guidelines included in the International Consensus [43]. These guidelines were developed in close association with the World Health Organization and have been endorsed by the International Diabetes Federation [43].

Additional system-based and behavior-based CER is needed in lower extremity diabetic foot complications and prevention. Through randomized clinical trials, it has been shown that intensive lifestyle interventions can be more effective than medication interventions in preventing the onset of diabetes over short-term follow-up. The Diabetes Prevention Program found that lifestyle changes were just as effective as medication after 10 years of follow-up in the prevention of diabetes onset [104, 105]. Other studies have found that lifestyle changes and intensive glycemic control of diabetes can prevent complications in those already diagnosed with the disease. Furthermore, improvement in glycemic control can also result in improved quality of life and economic benefits [64].

Summary and Concluding Remarks

Defining, measuring, monitoring, and improving the quality of health care is in a state of continuous evolution. There are intense efforts to improve the quality of health care, while reducing cost in the US Health Care Reform is currently a national priority in which the primary goal is to transform health care through improved quality, safety, availability, efficiency, transparency, and cost reduction. There is an emphasis on promoting preventive services, reducing quality gaps, advancing scientific knowledge through CER, and improving information technology capabilities [106].

The challenge to deliver the highest quality health care to patients with diabetes is complex and multifaceted. Federal, regional, state, and

private agencies, along with physicians and researchers, need to combine feasible yet meaningful and interpretable QIs into a single standardized information database to effectively and efficiently track changes in the quality of care. The burden placed on general practitioners and specialty physicians is great and will likely continue to increase. Despite the best intentions of physicians to provide the highest quality of care in patients with diabetes, a fragmented system sets everyone up for failure. Meaningful health care system changes are needed throughout major institutions and private practice. Strong leadership from appropriately trained physicians in health care quality is needed to ensure that there are positive and meaningful changes for both patients and physicians. Although our society will continuously debate the best course of action to achieve the highest possible health care quality in diabetes, efforts from all levels will continue until the diabetes epidemic and its associated complications are better controlled.

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Psychosocial and Educational Implications of Diabetic Foot Complications

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Abstract

In recent years, clinicians have begun to recognize the impact that educational, psychosocial, and behavioral factors have on treatment success for leg and foot wounds. Further, many now consider quality of life an important outcome of treatment for those suffering from neuropathy, foot ulcerations, and amputations. However, although interest is increasing, behavioral aspects of the diabetic foot remain emerging science. Researchers are only now beginning to investigate the psychological response to diabetic foot ulceration and amputation and the behavioral and psychological factors that influence self-care. Although cross-sectional studies have explored these areas, little longitudinal data currently exist.

In this chapter, we review the current state of behavioral science pertaining to individuals with diabetic foot disease including barriers to prevention, precipitating factors, and therapeutic interventions. The first section describes some of the behavioral/psychological issues faced by individuals with diabetes during the course of their illness. We describe four phases of psychological responses and attempt to relate these phases to the prevention, diagnosis, or treatment of foot problems. Then, we discuss quality of life for those with peripheral neuropathy, lower extremity wounds, or amputations. Next, we discuss depression, its impact on self-care, signs and symptoms, and implications of treatment. Finally, we describe measurement instruments, strategies, and interventions that may

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be useful for clinicians either to incorporate into their clinical practice or as a referral for struggling patients.

Keywords
Diabetic foot complications • Psychosocial implications • Educational implications • Quality of life • Self-care • Amputation

Introduction

In recent years, clinicians have begun to recognize the impact that educational, psychosocial, and behavioral factors have on treatment success for leg and foot wounds. Further, many now consider quality of life an important outcome of treatment for those suffering from neuropathy, foot ulcerations, and amputations. However, although interest is increasing, behavioral aspects of the diabetic foot remain emerging science. Researchers are only now beginning to investigate the psychological response to diabetic foot ulceration and amputation and the behavioral and psychological factors that influence self-care. Although cross-sectional studies have explored these areas, little longitudinal data currently exist.

In this chapter, we review the current state of behavioral science pertaining to individuals with diabetic foot disease including barriers to prevention, precipitating factors, and therapeutic interventions. The first section describes some of the behavioral/psychological issues faced by individuals with diabetes during the course of their illness. We describe four phases of psychological responses and attempt to relate these phases to the prevention, diagnosis, or treatment of foot problems. Then, we discuss quality of life for those with peripheral neuropathy, lower extremity wounds, or amputations. Next, we discuss depression, its impact on self-care, signs and symptoms, and implications of treatment. Finally, we describe measurement instruments, strategies, and interventions that may be useful for clinicians either to incorporate into their clinical practice or as a referral for struggling patients.

Phases of Psychology Responses and Educational Aspects of Diabetes

Individuals face significant events or crises at different points during the course of diabetes that challenge their usual ways of coping and dealing with stress [1–3]. These events evoke heightened anxiety, feelings of helplessness, and temporary states of cognitive confusion. People facing crisis typically employ coping strategies they have used in the past that have varying levels of effectiveness [1]. Some strategies such as denial or anger may actually interfere with health while other strategies using a more pragmatic approach serve to help incorporate information and skills into one's lifestyle [4]. Those living with diabetes face important stressors throughout the course of illness.

Four periods warrant special mention: onset of diabetes, health maintenance and prevention, early onset of complications, and the stage of illness where complications dominate [2, 3]. Each period has psychological and educational implications for the patient, family, and clinician regarding the prevention and treatment of foot problems.

Onset of Diabetes

The onset of diabetes is typically abrupt for those diagnosed with type 1 diabetes and for some diagnosed with type 2 diabetes. The patient and family, faced with the task of acquiring knowledge and "survival skills," must adapt quickly to a new and demanding regimen of insulin injections, blood glucose monitoring, nutrition, and other lifestyle adjustments. Both patients and families may

experience a period of grief and mourning for loss of the healthy self and begin to adjust to the idea of living with a serious chronic illness. Prior experience with diabetes, such as having a family member or friend who has the disease, can color the response to the diagnosis. During times of crisis, individuals have difficulty both processing and retaining information [1, 5]. Yet for most people with diabetes, diagnosis is the time when they receive diabetes education, and for many people, this education is the only formal education they receive during the course of their illness. Discussion of preventive measures such as foot care are often lost or simply not addressed when faced with the priorities of acquisition of "survival skills."

Onset of diabetes for those diagnosed with type 2 diabetes is typically more gradual and viewed as less cumbersome. Often, the perception of type 2 diabetes and treatment with oral medications for blood glucose control is considered a normal part of aging. Most individuals, if worried, are concerned about heart disease and hypertension, rather than their feet. Similarly, clinicians tend to stress more immediate concerns during their initial patient interactions. Prevention of foot complications is typically not addressed nor perceived as an immediate need by patients or clinicians.

Maintenance of Health and Prevention of Complications

During the maintenance phase, treatment and education focus on prevention of complications, healthy lifestyle habits, and incorporating changes in lifestyle into family life. Individuals with diabetes develop diabetes "habits", self-care behaviors that can include key preventive practices such as foot care. People tend to remember and do those things that they perceive as most important, typically those instructions that clinicians particularly stressed [6]. Unfortunately, not all physicians and educators emphasize the importance of foot care. Many clinicians do not check feet at each visit [7–9] but instead may focus on glycemic control in hopes that improved glycemia will prevent foot problems [10]. Intuition and some weak evidence suggest that preventive foot care education can decrease the incidence of ulceration and need for amputation [10–13]. Unless special effort is made to teach by example during office visits, preventive foot care will be largely ignored. Clearly, both patients and clinicians need education about foot assessment [14] and preventive foot care [13, 15]. Receiving education does not go hand in hand with the practice of self-care behaviors. Some patients may experience denial and resistance to treatment; these people typically have difficulty integrating preventive practices into their daily routines. Incorporating chronic illness into one's worldview takes time; health care personnel play key roles in coaching and assisting the patient to achieve this effectively.

Early Onset of Complications

Complications of diabetes develop insidiously. Most patients go through a period of years before being affected by microvascular and macrovascular complications. Although the concept of complications should not be foreign to patients with diabetes, the onset and recognition of complications sets a new disease trajectory affecting patients' relationships with family and providers and their self-image as a functioning, "healthy" person.

The prevalence of peripheral neuropathy is estimated to be 26–28.5% in patients with diabetes with most cases (62%) asymptomatic [16, 17]. Patients who lack protective sensation are seven times more likely to develop a foot ulcer secondary to physical and/or thermal trauma [18]. Treatment of neuropathy or its sequelae, foot ulceration and/or amputation, accounts for approximately 27% of medical costs attributed to diabetes in the USA [19]. Neuropathy is often first identified by either decreased reflexes or impaired localized sensation noted on routine examination of the feet; in most cases, both have gone unnoticed by the patient. At this point, intervention remains directed at maintaining circulation and skin integrity through heightened attention to foot care. However, for many patients, hearing this "bad news" engenders high levels of

stress and anxiety that serve to block the important communication occurring between provider and patient at this time [1]. Therefore, patients may be unable to effectively process what needs to be done to maintain their health. Furthermore, people often use the experiences of others to understand their own condition. Thus, patients may use the experiences of family and friends with diabetes to frame their assumptions about complications and may assume their own course will follow a similar path. Often these assumptions are not communicated to their health provider. Yet these beliefs and assumptions about diabetic neuropathy and its management are fundamental to motivation and performance of preventive foot care behaviors [20].

As neuropathy progresses, the patient is often faced with neuropathic foot pain which may be moderate to severe in intensity and difficult to control. Treatment is often not highly effective and patients must learn to live with discomfort that impacts their usual level of activity, ability to function, and sleep. Those with painful neuropathy may respond in one of two ways: maintenance of a high level of vigilance and a renewed interest in their health care practices which will facilitate preventive foot care or a more fatalistic response, "there's nothing I can do to control the course of events" which will inhibit motivation to perform preventive foot care behaviors [20].

Evidence suggests that the risk of foot ulcers and their associated cost of care could be significantly reduced by appropriate screening and targeted preventive strategies geared toward good foot care [11, 13, 21]. However, to be successful, these strategies must use a patient-centered approach in order to understand how patients make sense of and emotionally respond to diabetes since these are intimately linked to employment of self-care behaviors [22].

Complications Dominate

Foot ulceration affects 15–30% of patients with diabetes during their lifetime [23, 24] and complications of nonhealing ulcers include infection, gangrene, and amputation of the affected limb.

Table 25.1 Psychosocial consequences of foot ulcers or amputations

Reduced quality of life for both patients and caregivers
Depression
Alterations in self-image as a disabled person versus a healthy functioning person
Alterations in body image
Disruptions in family relationships
Dependency/over dependency
Alterations in social relationships
Social isolation
Sleep disturbances
Disruption in sexuality or sexual functioning

Foot ulcers are a causative factor in 85% of all nontraumatic lower limb amputations with resulting high morbidity and mortality [25]. Furthermore, those who undergo amputation are at higher risk to lose the remaining limb in the future [26]. Table 25.1 summarizes the psychosocial consequences of diabetic foot ulceration and amputation.

Diagnosis of a foot ulcer sets a new level of intensity to the patient's treatment regimen. Consultation with a specialist may be required for wound management. Patients will experience a double burden of illness—they still need to maintain or improve their self-care behaviors for management of diabetes but now need to perform complex wound care treatment regimens, establish relationships with new clinicians, and face new implications for both long- and short-term outcome. The patient may be unable to walk or drive a car, making that person dependent on others for office visits, dressing changes, obtaining treatment supplies, and routine activities of daily life. Sleep is disrupted by pain and discomfort [27, 28]. Treatment regimens are lengthy, complex, painful, and often require hospitalization. Research findings are inconsistent regarding the relationship between foot ulceration and psychological health. In one study of diabetic patients with foot ulcers, 68% reported negative psychological impact that included anxiety, depression, social isolation, and negative self-image [29]. In a more recent population-based study [30] of adults in Scandinavia, people with diabetes and

history of foot ulcers perceived their health and emotional well-being to be significantly poorer compared to those without diabetes. However, after controlling for potential confounding factors, levels of anxiety and depression and psychological well-being were similar for those with diabetes with and without foot ulcers. Negative emotions associated with ulcerations may be a response to the fear of amputation and frustration with the lengthy course of treatment and its uncertainty regarding outcome [27, 31, 32].

Adjustment to Amputation

Few studies have used longitudinal design to investigate the psychological response to amputations. Thus, we currently rely on cross-sectional data to understand factors that impact adjustment. Most of the studies that examine amputation include individuals with traumatic and medical amputations and thus are not diabetes specific. However, much of the information may apply to patients with diabetes. Phantom limb and stump pain may affect adjustment to amputation [33, 34]. Although phantom limb pain was originally viewed as psychosomatic in origin, current views hold that it also may have a physiologic basis [35, 36]. Phantom limb pain is common with one study finding 69% of persons with amputations experiencing this problem [37]. Whether psychological factors play any role in the origin of phantom limb pain is unclear. However, the presence of phantom pain may impede adjustment to amputation [34, 38] as reports have found it associated with depression [38–40], body image anxiety [38, 39, 41], and stress [33].

An individual with an amputation must cope with alterations in identity, with some viewing themselves as disabled versus healthy [33]. People with amputations will probably face the curiosity of society and the conscious or unconsciously labeling of "being different" [33–35]. These data suggest that helping individuals with a newly amputated limb prepared for societal response to their missing limb may be an important role for the health care team; patients need to know what to expect and anticipate how they feel and how they could respond.

Quality of Life

People value feeling well and most individuals place high priority on either maintaining or improving the way they feel. Neuropathy and its sequelae of foot ulceration and amputation diminish one's perception of self and feeling of wellness as these patients cope with neuropathic pain, wound management, and diminished mobility [28]. Treatment regimens for those faced with neuropathic pain are often complex and difficult for patients to understand, e.g., carefully titrated dosing, different medication combinations, and alternate uses of medications such as antidepressants for pain. Despite this, pain is often difficult to control. Further, treatment of foot ulceration is often burdensome, imposes additional mobility restrictions, and is of long and uncertain duration. In one study of quality of life for those with foot ulceration [42], the mean duration of ulcer treatment was 43 weeks and others have reported that approximately 70% of those receiving standard foot ulcer care will not heal after 20 weeks of treatment [43]. Although treatment duration is long, individuals with diabetic foot ulceration who seek timely care are more likely to heal today compared to those treated a decade ago [44]. However, promises of future improvement in health may not be a good motivator to follow complex treatment regimens when gains are associated with lifestyle restrictions of long duration and without guarantee of success [45].

Many people with diabetes feel burdened to some degree by the rigorous demands of their disease. Quality of life is a multidimensional concept representing an individual's physical, emotional, and social well-being from his own unique perspective [46]. Health-related quality of life and disease-specific quality of life refer to the impact of health problems on one's everyday life: examples include the effect of disease and its treatment on a patient's functioning, health beliefs, and subjective feelings of well-being [47]. As such, health-related quality of life is subject to change over time and over the course of illness.

Quality of Life and Self-Care

Clinicians need to understand patients' quality of life in order to understand their motivation or lack of motivation for self-care including wound care. Rubin [46] noted that those affected by what he termed "diabetes overwhelmus" or poor quality of life often take a "to hell with it!" attitude toward their self-care, doing less than recommended to manage their diabetes resulting in diminished self-care. Thus, assessment of quality of life issues is important, because it may powerfully predict an individual's capacity to manage his disease and follow treatment recommendations.

Assessing Quality of Life

Currently no gold standard exists for the assessment of diabetes-specific quality of life and a variety of instruments have been developed and used by researchers to understand the influence of glycemic control, treatment regimens, and complications on the person affected by diabetes. Diabetes researchers have used both general health and disease-specific quality of life instruments in order to appreciate the challenges of diabetes from the patient perspective. Diabetes quality of life (DQOL) studies have primarily focused on describing the health state of individuals with varying levels of symptoms and complications.

The use of intensive insulin regimens prompted interest in diabetes-specific quality of life and thus, in measuring diabetes patients' quality of life. The DQOL [48] measure was developed for use during the Diabetes Complications and Control Trial (DCCT) and subsequently adapted for youth [49]. DCCT found that intensity of diabetes treatment regimen does not, in itself, impair quality of life for those treated with intensive insulin regimens [50]. The Well Being Questionnaire [51] is another diabetes-specific quality of life measure developed for use in a World Health Organization study evaluating new treatments for the management of diabetes.

The PAID [52, 53] (Fig. 25.1) is both a clinical tool and an outcomes measure to identify diabetes-related emotional distress. Twenty items cover a range of emotional issues common among those with both types 1 and 2 diabetes. High scores indicate greater emotional distress and a score of greater than 40–50 merits referral to a mental health professional. The PAID strongly correlates with both depression and self-care [54] and is responsive to change over time [55]; thus, making it useful in assessment of patients undergoing long treatment regimens such as foot ulcer therapies. Identification of individual items of concern to the patient can serve as a point of conversation during the office visit.

General health related quality of life measures, i.e., not focusing on a specific disease such as diabetes, also provide information on quality of life in patients with diabetes. The EuroQol quality of life tool (EQ-5D) has two components: (1) a questionnaire that assesses mobility, self-care, usual activities, pain, anxiety, and depression and (2) visual analogue scale that allows patients to indicate their quality on a scale of 0–100 [42]. Functional health status is another important aspect of quality of life; the Short Form 36 (SF-36) is a well used measure in this area [56]. These measures, although not diabetes specific, allow comparison of quality of life issues for those with diabetes to both the general population and those with other chronic conditions.

Three recently validated instruments that reflect the emerging behavioral science are available to assess quality of life (NeuroQoL) [57], psychological predictors of foot self-care (patient interpretation of neuropathy—PIN) [58], and pain (brief pain inventory for painful diabetic peripheral neuropathy—BPI-DPN) [59–61] in patients with diabetic peripheral neuropathy. Clinicians may find these instruments useful for evaluating the clinical and psychosocial status of these patients. Table 25.2 briefly reviews the properties of the three instruments. In addition, Turk [62] proposes five screening questions, ACT-UP interview (activities, coping, thinking, upset, and people responses), as an efficient and brief approach in the assessment of important psychosocial and behavioral issues for patients with neuropathic pain. These screening questions focus on behaviors, patient coping approaches, pain prognosis, distress, and response to pain.

INSTRUCTIONS: Which of the following diabetes issues are currently a problem for you?
Circle the number that gives the best answer for you. Please provide an answer for each question.

	Not a problem	Minor problem	Moderate problem	Somewhat serious problem	Serious problem
1. Not having clear and concrete goals for your diabetes care?	0	1	2	3	4
2. Feeling discouraged with your diabetes treatment plan?	0	1	2	3	4
3. Feeling scared when you think about living with diabetes?	0	1	2	3	4
4. Uncomfortable social situations related to your diabetes care (e.g., people telling you what to eat)?	0	1	2	3	4
5. Feelings of deprivation regarding food and meals?	0	1	2	3	4
6. Feeling depressed when you think about living with diabetes?	0	1	2	3	4
7. Not knowing if your mood or feelings are related to your diabetes?	0	1	2	3	4
8. Feeling overwhelmed by your diabetes?	0	1	2	3	4
9. Worrying about low blood sugar reactions?	0	1	2	3	4
10. Feeling angry when you think about living with diabetes?	0	1	2	3	4
11. Feeling constantly concerned about food and eating?	0	1	2	3	4
12. Worrying about the future and the possibility of serious complications?	0	1	2	3	4
13. Feelings of guilt or anxiety when you get off track with your diabetes management?	0	1	2	3	4
14. Not "accepting" your diabetes?	0	1	2	3	4
15. Feeling unsatisfied with your diabetes physician?	0	1	2	3	4
16. Feeling that diabetes is taking up too much of your mental and physical energy every day?	0	1	2	3	4
17. Feeling alone with your diabetes?	0	1	2	3	4
18. Feeling that your friends and family are not supportive of your diabetes management efforts?	0	1	2	3	4
19. Coping with complications of diabetes?	0	1	2	3	4
20. Feeling "burned out" by the constant effort needed to manage diabetes?	0	1	2	3	4

Fig. 25.1 The Problem Areas in Diabetes questionnaire

Table 25.2 Psychosocial assessment tools for patients with diabetic peripheral neuropathy

Name	Items	Scale type	Subscales/dimensions	Psychometric properties
Quality of life				
NeuroQol [57]	43	5-point Likert scale; higher scores = poorer quality of life	Dimensions: (1) painful symptoms and paresthesis, (2) symptoms of reduced/lost feeling in the feet, (3) diffuse sensory motor symptoms, (4) limitations in daily activities, (5) interpersonal problems, (6) emotional burden, (7) overall impact of neuropathy, (8) medication side effects, (9) sleep disturbance	Validity: NeuroQoL physical symptoms associated with Neuropathy Disability Score ($P<0.001$); internal reliability: alpha = 0.86–0.95
Psychological predictors of foot self-care				
Patient interpretation of neuropathy (PIN) [58]	39	5-point Likert scale	Dimensions: (1) common sense beliefs about diabetic neuropathy (DN) and levels of understanding of DN-related medical information and (2) worry about potential consequences and anger at practitioners	Internal reliability = 0.62–0.90; test–retest reliability $r = 0.51$–0.64
Pain				
Brief Pain Inventory for Painful Diabetic Peripheral Neuropathy (BPI-DPN) [59–61]	11	10-point Likert scale with higher scores indicating greater severity or greater interference	Two subscales: Severity Scale (four items) and Interference Scale (seven items)	Criterion validity: moderate to strong correlation between BPI-DPN and three alternative pain rating scales; discriminant validity: moderate negative correlation between BPI-DPN subscales and SF-12; identification of cut points for worst pain and average pain: mild (0–3), moderate (4–6), severe (≥7)

Effect of Diabetes and Neuropathic Complications on Quality of Life

Only a few studies have specifically examined the effect of foot ulcers and amputation on quality of life and these have primarily used generic rather than diabetes-specific instruments.

In general, quality of life is lower for those with diabetes compared to those unaffected by the disease [30, 63]. Further, quality of life for type 2 diabetic patients without complications and not on insulin was slightly higher compared to those with uncomplicated type 1 diabetes; scores for those with diabetes were similar to scores reported in other studies for adults with chronic obstructive pulmonary disease and osteoarthritis [63]. Similar findings have been reported by others [64, 65].

Complications of diabetes are the most important disease-specific determinant of quality of life for diabetes patients [66]. Quality of life is diminished not only for those affected by neuropathy and its sequelae but also for their caregivers as well [53, 67]. Coffee [63] reported progressively lower quality of life scores for those with symptomatic neuropathy and ulceration with the lowest scores reported for those with amputation indicating the increased health burdens presented by these complications. However, others suggest that those treated for foot ulceration may experience poorer quality of life than those with amputation because of the fear of ulcer recurrence, repeated episodes of infection, and potential lifelong disability [29, 68].

Impact on Patient and Family

Qualitative studies using focus group [27] and in-depth interview [28] methodology offer insight into the experiences of those with foot ulceration and family members who participate in their care. Foot ulcers require the incorporation of a completely different lifestyle for both patients and their caregivers and have an equally negative impact on both the patient and caregiver. Reduced mobility and diminished sense of self restricts the patient's usual life regardless of age and has consequences on role function and sexuality. Although interest in sexual activity does not diminish [69, 70], many individuals with lower extremity amputations report problems such as loss of libido and erectile dysfunction [70, 71]. Because of problems with autonomic neuropathy, sexual problems may be more prevalent among individuals with diabetes. Loss of employment is a problem for many affected by ulceration or amputation [72], particularly those in occupations which require a great deal of walking or standing and is associated with reduced self-esteem especially for younger patients.

Restrictions in mobility are particularly hard for diabetic patient with foot ulcers. Patients are generally concerned with becoming a burden on others in terms of their daily care, shopping, cooking, and transportation to frequent medical appointments [27, 28]. Patients and their caregivers voice their perception of social isolation, patients because of the physical activity restrictions imposed by the ulcer, and family members because of the time and intensity burden of caring for their ill family member [27, 28]. One qualitative study reports [27] that despite their understanding that nonweight bearing would promote healing, nearly all patients could not comply either through necessity or frustration. The negative impact of foot ulceration on quality of life is pervasive for both patient and family and fraught with uncertainty about whether the ulcer will heal and, if so, whether it will recur in the future.

Implications for the Practitioner

Focusing attention on physical care of the feet without attention to the psychosocial features of health-related quality of life has important limiting effects on both patient care and strategies for intervention [28]. Greater understanding of quality of life specific to lower extremity ulcers by physicians is important to allow for improved patient–physician communication, adherence to treatment regimens, and increase in patient satisfaction and quality of care. Further, assessment of the impact of diabetes on the patient is important to identification of patients who may

have a more difficult time in either complying with the demands of more demanding self-care regimens, or may benefit from referral to a mental health professional for counseling. The Problem Areas in Diabetes Scale is particularly useful in this area.

Depression and Depressive Disorders

Depression is a serious psychiatric disorder that interferes with interpersonal relationships, quality of life, and the ability to perform and function. Both amputation and diabetes are independently associated with depression, placing these individuals at extremely high risk of depression and its consequences [73–75]. Depression may accompany amputation in the general population with older people experiencing more depression within the first 2 years following amputation and younger individuals experiencing more depression over the longer term [76].

Table 25.3 Symptoms of depression

Depressed mood
Loss of pleasure or interest in activities
Tearfulness and crying spells
Irritability[b]
Increased sense of worthlessness or guilt
Recurrent thoughts of suicide or death[c]
Suicide threats or attempts[c]
Loss of concentration[b]
Decrease in recent memory[b]
Fatigue; loss of energy[b]
Pessimism
Significant weight or appetite loss when not dieting; failure to gain age-appropriate weight[b]
Indecisiveness
Social withdrawal or isolation
Insomnia or hypersomnia[b]
Psychomotor slowing[b]
Psychomotor agitation

[a]Depressed mood and four other symptoms for over 2 weeks may indicate major depression
[b]Symptoms that may also reflect poorly controlled diabetes and/or hypoglycemia
[c]Suicidal ideation should treated as a medical emergency and assessed immediately

Diabetes and Depression

The prevalence of depression for people with diabetes is about 2–3 times that of the general population [74, 75]. Comorbid depression occurs in all age groups, and ethnic minorities experience depressive symptoms and depression at rates that equal those of adult Caucasians [77–80]. In addition, severity of depressive symptoms is associated with poor adherence to dietary recommendations and medication regimen, functional impairment, and higher health care costs in primary care diabetes patients [81]. High levels of diabetes-related emotional distress are associated with poor adherence to self-care behavior recommendations [54]. Thus, dysthymia, subclinical depression, and diabetes-related emotional distress can impact the success of diabetes treatment, diabetes self-care, and one's ability to care for their wound or amputation. Unfortunately, depression in diabetes is both under-recognized and, when recognized, under-treated [82–85]. Findings of a recent retrospective cohort study [86] suggest that depression is associated with a 33% higher risk of incident major lower limb amputation in veterans with diabetes and highlight the importance of screening, early diagnosis and treatment of depression.

To further complicate the picture, depression among people with diabetes is also associated with the presence of other serious complications: retinopathy, macrovascular complications of cardiovascular disease, neuropathy, nephropathy, hypertension, and sexual dysfunction [77, 87–90]. Thus, individuals with depression and peripheral vascular disease may also be coping with other serious comorbidities.

Depression may present with cognitive, physical, affective, or attitudinal symptoms. Table 25.3 lists symptoms that typically mark depression, although most people present with only some of these symptoms. The physical and cognitive symptoms often overlap with poorly controlled diabetes, making the diagnosis more difficult. Several short assessment tools such as the Beck Depression Inventory [91], the Hospital Anxiety and Depression Scale [92], or the Brief Symptom

Inventory [93] useful for screening for depression. Asking simple questions such as "during the past month, have you been bothered by feeling down, depressed or hopeless?" and "during the past month, have you been bothered by little interest or pleasure in doing things?" can be as successful as surveys when screening for depression [94]. If a person experiences depressed mood or loss of interest or pleasure in usual activities and at least four other depressive symptoms for a duration of at least 2 weeks, then major depression must be considered [95]. It should also be considered when these symptoms are accompanied by deterioration in glycemic control or the inability to function in the home or at work.

Treatment of Depression

Depressive disorders are usually responsive to treatment with medications or psychotherapy. Both treatments are effective used alone or in combination [87, 96]. Although the primary care provider typically initiates pharmacotherapy, knowledge of when to initiate a mental health referral is important [97]. Those with suicidal ideation are at serious risk and need immediate and appropriate referral psychiatric care. As depression improves and symptoms begin to remit, treated patients are more energetic and therefore may become at even greater risk of suicide. A mental health professional can also help (1) evaluate the success of current therapy, (2) institute combination therapy using counseling as well as medication, (3) individualize pharmacotherapy, and (4) evaluate the need for hospitalization.

Impact of Patient Education Interventions

Diabetes foot care education is particularly important given lower leg and foot complications can be minimized or prevented with proper foot care and periodic foot examinations [98]. Several prospective randomized controlled trials have evaluated the effectiveness of education interventions for the prevention of foot ulceration in patients with diabetes [11, 12, 99–106]. Most of these interventions demonstrated short-term improvements in foot care knowledge and behaviors, while few observed or assessed reductions in ulcer incidence and amputation rates.

Multiple systematic reviews have evaluated the effectiveness of these education interventions [107–111], concluding that there was limited evidence to support the effectiveness of patient education alone in preventing foot ulceration or amputation due to poor methodologic quality. Most of these studies were insufficiently powered, utilized unknown or unregistered co-interventions in the control group, and/or assessed foot care knowledge and behavior via subjective outcome measures [111]. Further, no studies examined the comparative effectiveness of education provided at different time points during the course of diabetes: at time of diagnosis, maintenance of health and complications, or at early onset of complications. More well done studies of interventions are needed to evaluate the effectiveness of patient foot care education in the prevention of foot ulceration and amputation. Further, randomized trials of treatment/prevention options should also include a clearly defined education component.

Strategies to improve Self-Care Behaviors

Several techniques are available for use by clinicians to help patients improve their self-care behaviors. This section describes these techniques, some of which can be easily incorporated into an office visit or other patient encounter.

Reinforcing Information

Most people remember only a small portion of the information that they receive during medical appointments. Studies that compared the information retained by patients after the appointment with the information that physicians gave patients during the appointment found that between 31

and 71% of information was forgotten [6]. Clinicians need specific techniques to reinforce important information for their patients who do not require large amounts of time and who help make the appointment more effective and efficient.

1. People tend to remember those things that are presented first, thus during the visit, discuss the most important points first.
2. Those things that are perceived as important are remembered better. Thus, when discussing a key point begin by saying: "This is very important…"
3. Simple, clear instructions are remembered better than complex or confusing instructions.
4. Be specific and concrete rather than vague. For example, "Take off your socks and check your feet and between your toes every day" is more specific and easier to follow than "Be sure to check your feet".
5. Information, particularly key points or take home messages, written down in simple terms helps reinforce learning and information retention.
6. Ask patients to prepare for their medical appointment by writing down all questions that arise during the week prior to the appointment and bring that written list to the office with them. This approach is a very efficient way to assess the patient and answer outstanding questions. People tend to remember information about issues that they have previously considered and that directly relates to them or their health.

Diabetes Education Handouts

Diabetes foot care education handouts are useful for reinforcing important self-care information and reminding patients on the specific techniques necessary to identify and prevent potential problems. Most patients remember only a small portion of the information that they receive during medical appointments, thus a handout is an effective and inexpensive way to reinforce important information. Table 25.4 provides characteristics of effective handouts.

Table 25.4 Characteristics of effective diabetes education handouts

- Simple and easily understood: simple and easily understood information is more likely to be read and followed by the patient
- Concise information: concise information is more likely to be remembered
- Portable and functional information: easily accessible information that incorporates additional functions (e.g., calendar, wallet-size card) is less likely to be put aside and/or forgotten
- Necessary and sufficient information: handouts require appropriate information that promotes patients' self-care practices
- Positive and encouraging information: information should support patients' efforts to perform self-care, not offend or discourage them
- Consistent information: information provided in the handout should be consistent with other information the patient receives. For example, consistent information across education classes, one-on-one counseling, reading materials, etc.
- Good mix of text and graphics: visually appealing information will enhance the messages contained in the handout

Interview Techniques to Help Patients Who Struggle with Their Self-Care

Motivational interviewing [112, 113] incorporates standard interviewing techniques in a process that is designed to help individuals who are struggling with health issues get back on track with their self-care. This technique, originally developed in the addictions field, provides a useful platform for busy clinicians to address barriers in an effective, simple manner.

Open-ended questions allow the patient to verbalize feelings and provide information in their own words thus preventing the clinician's preconceived ideas to dictate patient responses. "Tell me about…" "How are you doing with taking your medications?" "What is it like to wear the orthotic?" and "What problems are you having taking care of your diabetes?"

Although questions such as "How are you doing?" and "How do you feel?" appear open-ended, they are vague and have also taken on a social context that precludes more than a superficial response of "Fine".

Active listening entails consciously focusing on what the person means. This is not as easy as it sounds. Although everyone listens to some extent, busy clinicians may develop a preconceived idea of what the person means. Many people tend to think about what they will say next instead of focusing on what the patient is actually saying. Two useful tools for listening are reflection and summarizing:

1. *Reflection*: Repeat or paraphrase statements back to the person but using the tone of a question. "You are having trouble with your exercise plan?" "You are frustrated with your treatment recommendations?"
2. *Summarizing*: Summarizing the general idea of the patient's conversation shows that you have been listening and that you understand what the patient means. This technique also provides an opportunity to correct any misunderstandings. If the patient has outlined a plan or made other positive steps, summarizing can help reinforce their progress.

Conclusions

People with diabetes diagnosed with complications are at increased risk for diabetes-related distress and depression. Distress and depression impact the patient's ability to carry out self-care behaviors and follow through with treatment recommendations. This inability may limit success of regimens designed to prevent and treat foot ulceration. We offer some psychosocial, communication, and education strategies that can be employed by physicians and other caregivers and describe several clinical assessment tools to identify patients who are having quality of life issues and who may benefit from referral to a mental health specialist for additional counseling and/or pharmacologic intervention to help patients and family members obtain the most benefit from office visits.

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The Role of Footwear in the Prevention of Diabetic Foot Problems

26

Luigi Uccioli and Claudia Giacomozzi

Abstract

While it is true that the foot represents the human interface with the ground, and that its anatomical structures, in particular its numerous joints, ligaments, and muscles are designed and optimized to receive and manage the outcomes of forces and torques due to the action of gravity on the entire human body, it is also true that, at least for civilized populations, footwear—alone or in conjunction with insoles—indeed represents the final interface with the ground.

Shoes are thought, designed, and constructed to deal with a lot of factors, the most important of which should be the performance of a comfortable progression action while maintaining as much as possible the biomechanics of a physiological gait. Often, other factors like cost and fashion do interfere with the above aim and lead to solutions which are uncomfortable and, on a longer time scale, which represent the main cause for the onset of relevant and potentially dangerous changes in gait.

This is especially true for diabetic patients with long-term complications, such as peripheral neuropathy, that deeply influence physiologic gait and make the patient vulnerable and at risk of foot ulceration. Unsuitable footwear may precipitate this condition and may be responsible for the appearance of a foot ulcer.

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While it is true that the foot represents the human interface with the ground, and that its anatomical structures, in particular its numerous joints, ligaments, and muscles are designed and optimized to receive and manage the outcomes of forces and torques due to the action of gravity on the entire human body, it is also true that, at least for civilized populations, footwear—alone or in conjunction with insoles—indeed represents the final interface with the ground.

Shoes are thought, designed, and constructed to deal with a lot of factors, the most important of which should be the performance of a comfortable progression action while maintaining as much as possible the biomechanics of a physiological gait. Often, other factors like cost and fashion do interfere with the above aim and lead to solutions which are uncomfortable and, on a longer time scale, which represent the main cause for the onset of relevant and potentially dangerous changes in gait.

This is especially true for diabetic patients with long-term complications, such as peripheral neuropathy, that deeply influence physiologic gait and make the patient vulnerable and at risk of foot ulceration. Unsuitable footwear may precipitate this condition and may be responsible for the appearance of a foot ulcer.

To better understand the criteria which should be taken in mind when prescribing or making proper footwear and/or plantar orthoses, a short summary of the main effects of diabetes and diabetic complications is here reported with a special attention to the role of these changes in the altered foot biomechanics.

The Effect of Diabetes on the Main Structures of the Foot–Ankle Complex [1–5]

Here, below the main foot structures are taken into consideration whose care is of special interest in any preventive or therapeutic action delivered through shoes and insoles:

Effects on tendons and ligaments: due to protein glycosilation and the consequent collagen abnormalities, tendons, and ligaments show greater transversal sections than usual; the thickening, which increases in relationship with the severity of the disease, i.e., disease duration, metabolic control, contributes to the increase of the stiffness of these tissues, i.e., greater coefficient of elasticity. This process is particularly evident in Plantar Aponeurosis and Achilles Tendon, both structures playing a critical role in the performance of gait.

Effects on cartilage: the characteristics of healthy cartilage result in an essential help to gait and standing, i.e., range of motion of each foot and ankle joint is easily maintained due to well-lubricated bone interfaces, and an accommodative action is done in standing which helps to maintain balance of leg bones over the talus with a minimum involvement of muscular structures. Similarly to tendons and ligaments, diabetic foot cartilage changes its composition mainly due to the modification of collagen fibers; this increases its stiffness and represents an obstacle in the performance of physiological range of motion of each and every foot and ankle joint.

Effects on muscles: diabetes mellitus entails a severe damage to nerve conduction, thus causing a worsening in the management of the related muscle fibers; as a consequence, both intrinsic and extrinsic muscles of the foot–ankle complex are damaged as for structure (reduction of muscle volume) and function (reduction of muscle strength); more specifically, a reduced function of tibialis anterior leads to a poor control of foot landing at heel strike and of toe clearance at toe-off, while a reduced function of intrinsic muscles entails a poor stabilization of foot bones and arches during loading acceptance and propulsion and a significant unbalance between muscle and ligament actions during the entire phase of stance.

Effects on peripheral sensory system: peripheral neuropathy impairs significantly peripheral sensory system. It leads to a loss of protective sensation under the sole as well as on the dorsum of the foot. This exposes the foot to thermal or mechanical trauma, and to the late detection of tissue breakdown and superimposed infection processes.

Effects on skin: the skin and the soft tissues immediately underneath the skin of a diabetic foot are stressed by compressive loading greater than normal, as well as by shear forces higher than usual both under the foot sole and on the dorsum of the foot. The abnormal load related to both vertical forces and shear stress may induce tissue damage starting from the inner part of the skin and soft tissue, explaining from a mechanically point of view why the onset of ulceration processes is so deeply related to traumatic tissue damage. Besides this, skin of the diabetic foot suffers from loss of autonomic control and a consequent reduced hydration, which makes it less elastic and thus more vulnerable to the action of increased mechanical stress.

Effects on foot morphology (deformities): due to most of the above alterations, and the above significant unbalance between peripheral musculature and soft tissue, the diabetic foot undergoes to serious alterations of its morphology and to the onset of foot deformities. Most common deformities of the diabetic foot are represented by a high longitudinal arch (rigid cavus foot), hammer toes, and hallux valgus. Foot deformities are responsible for the frontal shift of the submetatarsal adipose pads, following which the metatarsal heads come into direct contact with the ground [6]. It is in this situation that the development of hyperkeratosis which is a response mechanism to the overload, is in itself responsible for further hyperpression (indeed, it has been ascertained that the removal of a hyperkeratosis is able to reduce hyperpression up to 30%) [7]. Finally a rigid foot, thus less adaptable to the floor during the foot–floor interaction, develops; it remains rigid during the whole walking cycle thus leading the appearance of the high plantar pressures. A relationship between plantar fascia thickness and forefoot increased vertical forces has been established thus supporting that soft tissue abnormalities may contribute to the development of a different pattern of pressure distribution under the foot [8].

Some prospective studies have also demonstrated the relationship between areas of hyperpression and the subsequent development of ulceration [9]. It should also be borne in mind that an increase in pressure associated with insensitivity represents an increased risk; indeed, subjects with rheumatoid arthritis with comparable hyperpression do not experience ulceration [10]. Therefore, it is fairly evident that a reduction in hyperpression represents a means of reducing the risk of ulceration.

Proper Footwear: Special Needs for Diabetics

The above effects become more and more evident as the long-term complications, such as sensory and motor neuropathy, are fully developed. However, all potential effects and changes should be taken into account even at a mild level of complications, when the patient still does not have the need for a specific custom-made footwear prescription. In early, mild-level stages of peripheral neuropathy, in fact, as much as possible should be done not only to cope with, but also to prevent or delay the onset of biomechanical

alterations. The choice of a proper footwear, together with a strong education program, can be effective in addressing such issues. Several studies support the belief that inappropriate footwear causes ulceration. It is fairly obvious that given their vulnerability, diabetic subjects must select footwear which does not pose a further threat of risk and which ideally should serve as a form of protection. It is important that the physician, conscious of the importance of the role of footwear, be fully informed in order to make suitable recommendations. In turn, the patient must be made aware of the potential risk of lesion posed by unsuitable footwear, and must be encouraged to accept selecting a certain type of footwear which may not necessarily coincide with personal taste.

At a late stance, when patients are seriously compromised, and the prevention of ulcer formation or recurrence is of primary importance, main function asked to proper footwear is surely accommodative and protective rather than corrective.

Independently from the level of peripheral neuropathy, key common elements for the choice of proper footwear are: (a) redistribution of plantar pressure in order to avoid high localized peaks; (b) reduction of friction; (c) prevention of mechanical and thermal traumas; and (d) restoration or maintaining of foot function during gait.

A certain consensus has been reached on the main criteria for footwear design and prescription according to the presence and severity of the diabetic neuropathy.

Categories of Risk and Footwear Recommendations

Not all patients have the same level of risk to develop foot ulcers, and a number of factors, including the presence/absence of protective sense perception, presence/absence of significant foot deformities, presence/absence of previous ulcers, eventual simultaneous presence of more complications should be evaluated in determining risk categories and planning corrective means of prevention [11].

Four risk categories have been identified on the basis of these criteria (Table 26.1).

Table 26.1 Risk classes

0 Low	Patients with normal protective sensation
1 Medium	Loss of protective sensation, without foot deformities and without history of foot ulceration or previous amputation
2 High	Loss of protective sensation, with foot deformities but without history of foot ulceration and/or amputation
3 Very high	Loss of protective sensation, with foot deformities and with history of foot ulceration or amputation

Fig. 26.1 Shoes with soft sole and amply shaped soft upper available in different widths suitable for risk classes 0 and 1

Category 0: Patients Not at Risk of Ulceration (Primary Prevention)

These patients do not have active or previous lesions, nor chronic complications, and maintain a protective sensation. They require adequate education, but no real change to footwear for daily use, unless they are using too tight or too high-heeled shoes. In general terms, given their diabetic status, they should be simply encouraged to evaluate a number of factors when selecting footwear, most important of which whether the shoe is well-fitting. It must be kept in mind, in fact, that too narrow shoes act with high friction on the foot skin, both on the plantar surface and on dorsum, but too large or too long shoes also entail high friction due to the undesired relative movement between the foot and the shoe. Patients should thus avoid tight-fitting footwear with narrow forefoot, tight toe box or tight instep, while they should look for amply shaped shoes with soft uppers and a sole able to absorb vertical forces (Fig. 26.1).

Table 26.2 Suggestions for the right selection of footwear

• Both feet should be measured with an appropriate measuring device
• Both shoes should be fit while standing
• The position at the first metatarsophalangeal joint should be checked. It should be located in the widest portion of the shoe
• The right length of the shoe should be checked; additional volume should be considered at the top of the toes. Allow 3/8 to ½″ between the end of the shoe and the longest toe
• The proper width should be tested; enough space should be present around the ball of the foot. A soft and moldable upper with extra space should be selected in the presence of foot deformities
• A firm heel counter for rearfoot stability with a soft padded collar
• Shoes with laces or straps should be selected because they allow a wider open and an easier entry into the shoes, and in addition they allow a better fitting with the foot shape

Shoes made at least with different widths for each size should be preferred in order to better fit the natural shape of the foot without constriction.

Custom-made inserts are usually not necessary with these patients.

Education on selection of suitable footwear is very important. Table 26.2 shows some basic suggestions for the correct selection of footwear.

Fig. 26.2 Oxford, soft flexible leather laced shoes of adequate size to accommodate pressure—dissipating accommodative insoles

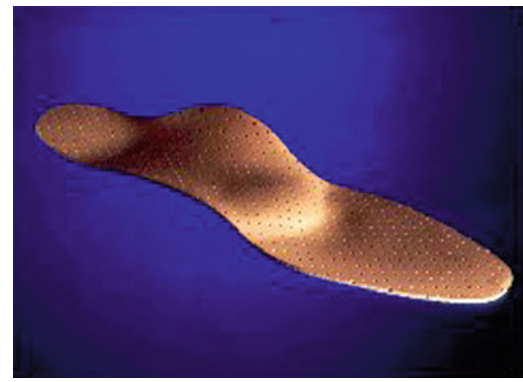

Fig. 26.3 Single layer, pressure—dissipating accommodative insole

Category 1: Patients at Medium Risk of Ulceration (Primary Prevention)

These patients experience a sensory neuropathy with an ensuing loss of protective sensation and a subsequent risk of ulceration. Education to a proper foot care and a proper footwear selection is extremely important for these patients. First of all, they must avoid walking barefoot, avoid wearing mended socks, and learn to substitute the loss of sensation with alternative senses (e.g., eyesight or hand touch). When sensation is lost, thermal damages may occur as well as mechanical traumas, thus they must learn to sample water temperature by hand before washing their feet in order to avoid burns, to detect foreign bodies, such as pebbles before putting on their shoes, and to evaluate other dangerous signs (e.g., tacks or worn soles).

Even if no studies have tested the efficacy of footwear in the primary prevention of ulcers, the patients must be guided to an understanding that the selection of footwear cannot be based on the usual criteria, namely the immediate sensation of comfort. Indeed, in the presence of sensory neuropathy, the patient perceives even tight shoes to be comfortable. Therefore, it is essential that the foot be measured in all its dimensions and that the footwear contain the foot without even the most minimal constriction. Education in the selection of the shoes is therefore very important in this category as well (Table 26.2). Soft leather laced shoes of adequate size to accommodate pressure—coupled with dissipating accommodative insoles—should be preferred (Figs. 26.2 and 26.3). Shoes and inserts should however allow the maintenance of a physiological gait [12].

Category 2: Patients at High Risk of Ulceration (Primary Prevention)

When the loss of protective sensation is complicated by foot deformities (e.g., bunion, claw toe, and hammer toe) whether independent of diabetes (e.g., idiopathic bunion) or more frequently secondary to motor neuropathy, the risk of ulceration is considerably increased [13].

In those cases where foot deformities (e.g., of the toes) are accommodated in unsuitable footwear, the mechanism underlying the lesion involves friction caused by the upper part of the shoe which in the first instance determines a superficial abrasion and later an outright ulcer. Ulcers associated with this sort of friction are usually localized on the top of the toes and on the lateral surfaces of the first and fifth toes. According to Eurodiale data toes are the most frequent place where the ulcers do develop [14]. These cases necessitate a heightened awareness of the correct selection of footwear both in terms of shape, as the foot should not be constrained in any way, and from the point of view of materials used for the uppers. These materials should be soft and flexible, as well as adaptable to any surface irregularities in such a way as to guarantee perfect fitting and to avoid the threat of friction. Nonetheless, the increased risk associated with foot deformities is not exclusively due to the difficulty in accommodating deformed toes, but above all to the biomechanical changes in gait pattern provoked by such deformities. Among the most evident and most important changes, it is worth to note: poor control of landing and propulsion due to a weaker tibialis anterior; loss of stability due to atrophy of the lumbrical and interosseous muscles [15]; forward shifting of the metatarsal head pads with exposure of metatarsal heads due to unbalance between muscle and ligaments stabilization action; reduction of joint mobility at the foot and ankle joints; alteration in the walking pattern shifting from an ankle-based to a hip-based walking strategy [16]; appearance and persistence of overload at the metatarsal level in the propulsion and toe off phases due to most of the above effects [17, 18].

Fig. 26.4 Section of a shoe with "biomechanical properties": the recessed heel allows a soft impact at heel strike; the point of rolling inserted immediately behind the metatarsal heads allows a smooth transition from midstance to propulsion; the presence a wider angle between the sole and the ground at the most anterior part of the shoe further reduces the stress at the level of metatarsal heads during propulsion and toe off

Patients in this category benefit greatly from the use of footwear which enables the correction or at least mitigation of as many as possible of the above biomechanical defects [19]. Main footwear recommendations are summarized here below:

- Shoes with "biomechanical properties" should allow the development of a protected walking pattern, with reduced plantar pressures. This may be guaranteed by a total contact between the foot and the internal part of the shoe—usually obtained by custom accommodative foot orthoses—along the entire stance phase, and by using specific rocker bottom soles that allow an adequate impact at heel strike and—through a pivot point inserted immediately behind the metatarsal heads or, in any case, placed just proximal to the area in which pressure relief is needed—a smooth transition from midstance to propulsion; finally, a wide angle between the sole and the ground at the most anterior part of the shoe further reduces the stress at the level of metatarsal heads during propulsion and toe off (Fig. 26.4) [20].
- Many off-the-shelf walking and running shoes have a mild rocker sole which is quite effective at reducing plantar pressures in the forefoot and at delivering some metatarsal head relief and gait assistance; however, the pivot point might not be properly placed and the flexible sole might not be effective for a foot at high risk.

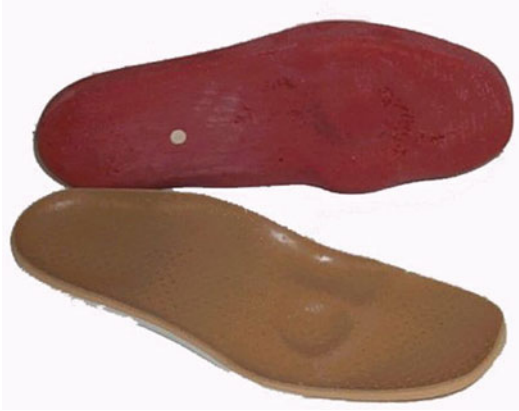

Fig. 26.5 Total contact, custom-fabricated, pressure-dissipating accommodative foot orthoses

Fig. 26.6 Footwear with a rigid rocker sole. The rigid sole minimizes the metatarsal–phalangeal joint articulation tension and maximizes foot contact area during late stance phase

Fig. 26.7 Total contact inserts can reduce pressure peaks under the foot by maximizing the contact area and spreading the pressure over a larger plantar surface

- Shoes should always be extra-depth shoes, so as to accommodate custom-made total contact inserts (TCIs).
- When the main issue to be addressed is the reduction of peak plantar pressures—i.e., patient is not yet compromised as for other biomechanical aspects like poor joint mobility or muscle performance—some running shoes designed for maximal forefoot pressure relief are effective in decreasing plantar pressure, especially when used in conjunction with viscoelastic insoles (Fig. 26.5); it must however be noticed that viscous materials, while representing excellent dampers to absorb shocks and high load, partly dissipate the energy that is instead released by proper elastic material during propulsion; thus, they should be used with care in case patients show a weak propulsion.
- Rigid sole better reduces forefoot pressures when compared with a flexible sole, since it maximizes foot contact area during late stance phase. When designing this kind of footwear, it is important to consider the position of the pivot point (rolling point of the step): a pivot point placed immediately behind the metatarsal heads usually guarantees for a reduction of peak pressure up to 30% (Fig. 26.6), with a potential further 20% of reduction made possible by the materials and the number of layers of customized inserts (Fig. 26.7).
- In any case, a common rule is simply never to use the same footwear for prolonged periods of time. Frequent change of footwear puts less stress on discrete areas of the skin and consequently reduces the risk of ulceration.
- Finally, there is a need for an appropriate unloading absorbed by total contact, custom-fabricated, pressure-dissipating accommodative foot orthoses inserted in deep lacing shoes manufactured in soft leather with a frontal region designed to suitably accommodate claw or hammer toes.

Category 3: Patients at Very High Risk of Ulceration (Secondary Prevention)

This category includes patients who have already had an ulcer which has healed. Diabetic patients with a history of relapsing plantar ulcers or patients with a previous minor amputation have abnormally elevated pressures under their feet during walking. Peak pressures most often occur under the metatarsal heads and correlate with sites of ulceration, and the risk of relapse is high indeed, up to 50% in a year. The reduction of

Fig. 26.8 Shoe with a rigid rocker sole and very high toe box to content deformed toes and multilayered customized insole

peak pressure through the use of appropriate footwear and plantar orthoses, as well as the restoration of a safe gait and the protection of the foot or the residual foot represent very important aspects in an effective program of treatment of the neuropathic foot (Figs. 26.7 and 26.8).

In terms of recommendations for the selection of footwear for this group of patients, the principles outlined for patients with peripheral neuropathy hold true for this category as well. In particular, patients should be encouraged to select footwear with rigid rocker soles and molded insert, preferably multilayered insofar as this type is most beneficial in reducing peak pressures.

In contrast to primary prevention, various studies have demonstrated the protective effect of footwear in secondary prevention and a consequent reduction of rate of relapse, both in terms of bespoke solutions and prefabricated commercially designed models. Among advantages and drawbacks of the former with respect to the latter, it is worth to mention the better fitting and the optimization of the accommodative and therapeutic solutions (advantages), as well as the higher cost, the longer delivery time and the limited adaptation to fashion (drawbacks).

However, for a clear demonstration of the evidence of the intervention effectiveness, a greater level of standardization is requested. The Consensus Development Conference on Diabetic Foot Wound Care, in fact, generically reported that "Footwear should be prescribed, manufactured, and dispensed by individuals with experience in the care of diabetic foot" [21]. Even Medicare guidelines, related to the Therapeutic Shoe Bill (TSB), do not clearly define qualifications of who has to furnish therapeutic footwear, while it gives indications about the type of footwear and plantar orthoses which can be prescribed and reimbursed in case of diabetic foot pathologies. Basically, the TSB Medicare (Part B) [22] states that a Diabetic patient may receive annually Medicare reimbursement for one pair of adjustable depth shoes or of custom-molded shoes, and three pairs of multidensity inserts. According to the document, an *adjustable depth shoe* is one that (1) has a full length, heel-to-toe filler that when removed provides a minimum of 3/16″ of additional depth used to accommodate custom-molded or customized inserts; (2) is made from leather or other suitable material of equal quality; (3) has some form of shoe closure, such as laces or Velcro; and (4) is available in full and half sizes with a minimum of three widths to assure a proper fit. A custom-molded shoe is one that (1) is constructed over a positive model of the patient's foot, (2) is made from leather or other suitable material of equal quality, (3) has removable inserts that can be altered or replaced as the patient's condition warrants, and (4) has some form of shoe closure, such as laces or Velcro. Inserts for diabetics, then, should be multiple density inserts, direct formed, molded to foot after external heat source of 230°F or higher, total contact with patient's foot, including arch, base layer minimum of 3/16″, material of Shore A 40 durometer (or higher), eventually including arch filler and other shaping material, custom fabricated.

Specific Needs in the Presence of Partial Amputation [20]

In case of partial amputation of a diabetic foot, it is essential to work to restore stability and function, facilitate energy-efficient gait, maintain support, and prevent any further complications.

It is essential to provide appropriate footwear and custom-made foot orthoses or prostheses. Basically, the criteria explained and reported here above also apply to this kind of foot, even though

some peculiarities must be taken into account, like the altered foot proportions, eventual increase of volume consequent to the surgical intervention, the loss of the propulsive lever represented by metatarsals and toes. Just for this reason, in a partial foot amputee, the solution of the rigid rocker sole with a proper pivot point proximal to the amputation and an adequate forefoot angle is the logical way to progress COP anteriorly past the distal end of the residual foot.

Abnormal plantar pressure and shear can be addressed and alleviated with custom foot orthoses. Lower limb orthoses or ankle foot orthoses (AFOs) and prostheses may help restore functional gait; more specifically, AFOs can be utilized to replace the lost lever arm of a transmetatarsal or hallux amputation: usually, a special insole is suggested containing an extended spring shank made of steel or carbon graphite composite (lighter but less robust). The shank keeps the shoe from bending, thus reducing forces through midfoot and forefoot (continuity of rocker sole). Partial foot prostheses, even though receiving great acceptance from the patients, needs to be used cautiously in patients with diabetes because of the presence of PAD and/or neuropathy: usually, they consist of silicone or acrylic resin partial foot prostheses (i.e., Chicago boot or a Lange prosthesis) which show good cushion, stability, and excellent reduction in shear forces and which result cosmetically pleasant; as a drawback, they present some difficulties to put on and off, they tend to be hot and not to permit air circulation and to macerate the skin and allow the growth of bacteria.

Shoes should be easily modifiable: soles made of EVA (ethylene vinyl acetate), neoprene or injection-molded polyurethane are easy to be worked; leather sole shoes are not difficult to modify but can become heavy and cumbersome when modified adding lifts, shanks, or rocker soles; rubber sole shoes are not easy to modify, as difficult are those shoes with extraordinary shock-absorbing features like air bladders, pockets of gel, or springs. As for each neuropathic patient the upper portion of the shoe should be made of material which is moldable, stretchable, and breathable like leather. The interior lining should be made of supple leather. Useful are also lining materials that wick moisture away from the skin, such as Gortex, or have antibacterial properties like X-static. High top shoes tend to work well for patients with transmetatarsal, Lis Franc, and Chopart amputations. Blucher opening should be preferred to a balmoral opening (adjustability and space across the instep and forefoot areas). A lace-to-toe or surgical opening might be preferred but usually not well accepted. Slip-on shoes should be avoided as most are tight and restricting, and do not cover enough of the dorsum of the foot.

For the partial amputated foot, a custom-made short shoe may work better (functional, effective, and comfortable) but it may be esthetically unacceptable. Full-length shoes with a rigid rocker sole are recommended.

Footwear in Charcot's Foot

Charcot's foot is characterized by complications of bones and joints of the foot in patients with diabetes and peripheral neuropathy. However, this is not always the case as the condition may occur in other forms of neuropathy, such as siringomielia, tabe dorsalis, etc. A clear case of Charcot's foot is characterized by a complete involvement of the bones and joints structures and the loss of the structural organization of the foot. In its most typical form involving the tarsal bones, there is a collapse of the foot arches and of the plantar roof; the foot then changes its proportion, becoming shorter and squat and the plantar surface assuming a rocking profile; as a direct consequence of these dramatic morphologic changes, there is the onset of very high pressures at mid foot, and the area becomes at risk of ulceration [23] both for the objectively high level of stress and, even worse, because this area is not "designed" to support high loads (as is instead for heel and metatarsal area). Corrective intervention in these patients involves diverse phase-related options. In the less dramatic case in which the bone involvement is detected before bone collapse, the use of a plaster cast, followed by a corrective strategy involving the use of a plantar support of the arch which enables the stabilization of the lesion, it is able to prevent the structural damage

to the foot. In other cases, a diagnosis is made when the bone structure has already deteriorated and the tarsal bones have lost their shape. The use of a plaster cast is necessary also in this case at least until the lesion has been stabilized; in some cases, it may take up to 6 months, associated with empirical observations of the skin temperature. Subsequent corrective strategies will largely depend on the ensuing structural deformity, insofar as if the patient is able to wear shoes, albeit customized footwear, surgical intervention may not be necessary while surgery is usually indicated otherwise. Corrective strategies aim at reducing plantar high plantar pressures and subsequently the risk of ulceration: as for footwear, rocker sole shoes should be used by the double rocker sole is recommended which, opposite to what all the other rocker soles do, redistribute plantar pressures while offloading the mid foot area. Using proper footwear, even commercially available therapeutic footwear and custom foot orthoses, more than half of patients with Charcot arthropathy at the mid foot level can be successfully managed without surgery [24].

Aids for Patients with Active Lesions

As we have already highlighted, patients with peripheral neuropathy tend to develop ulcers at the point of maximum load. Often patients are not able to, and they should not, stay in bed for 4 or 6 weeks, which is ideally the time required to heal an ulcer in patients with normal arterial circulation and an absence of significant complications (e.g., overlapping infections).

Often neuropathic ulcers do not heal due to the continued load placed on the ulcer during walking. It is fundamental in these cases to provide for an adequate unloading in order to favor healing [25]. Several options are available to ensure unloading in patients with active ulcers [26] (Table 26.3).

Total contact cast is the most extensively studied technique; it offers total unloading of the ulcer as well as the rapid mobilization of the patient who may resume normal activities immediately. As shown in several recent studies, total contact cast has become the gold standard for the treatment of diabetic foot ulcers [27, 28]. It allows the immobilization of the tissues of the ulcers; it reduces the pressures through a distribution over a wide surface. However, the use of the total contact cast must follow specific indications (neuropathic lesions in the absolute absence of infections) and contraindications (ischemic lesions and infected lesions; furthermore, their use is contraindicated in blind patients and in those with pathological obesity or ataxia) [29].

Table 26.3 Options to unload a neuropathic foot ulcer

• Total contact cast
• Other casts/boots (air cast, StabilD, optima, and walking cast)
• Temporary shoes

These plaster casts cover the lesion and are removed and substituted weekly in order to ensure a better fit as the edema withdraws and to inspect the wound.

Alternatively, one may use the scotch cast, a sort of removable boot made of stiff, light material padded with wadding in order to reduce pressure. This procedure is suitable for elderly persons who do not tolerate the plaster cast or in those cases where ulcers are situated in difficult areas. Indeed, the scotch cast is a sort of compromise between the plaster cast and other aids, as they are made-to-measure and easily removable [26, 30].

Other commercial techniques involve the use of stirrups or other pneumatic means of subpatellar unloading (air cast, walking cast) (Fig. 26.9). The high cost of these aids has prohibited their widespread use; moreover, their results do not seem to be more beneficial than those reported for the plaster cast [31, 32]. One of the limits to use these walking casts is the low patients' compliance. In fact, the easy removability may allow patients to wear it only in certain occasions. On the other hand, this special feature makes their use possible also in clinical conditions where it is necessary to follow strictly the lesion. To solve this problem, Armstrong et al. [33] have proposed the use of the "instant" total contact cast that is a walker rendered nonremovable by wrapping it with cast material. This solution can have all the advantages of the walker without the disadvantages related to a poor compliance.

Fig. 26.9 Aircast: this device allows a good control of high pressures at the ulcer site by means of subpatellar unloading

Fig. 26.10 Optima: offloading device

Other walking casts have been tested recently with good results in terms of clinical outcomes. These are Optima boot (Fig. 26.10) and Stabil D (Fig. 26.11). Both have clinical outcomes similar to that of total contact cast [34, 35].

Nonetheless, the plaster cast is unsuitable in some conditions. Other aids must be used in these cases, namely temporary shoes as talus shoes which enable an unloading of the lesion in the forefoot due to the absence of a sole in the front part of the shoe (Fig. 26.12). Using this healing device, the patients walk by loading only the rear foot. This type of footwear is particularly indicated in young persons who do not present problems of equilibrium. Other aids include temporary footwears with extra volume (extra deep 1/2″ or super deep 3/4″) and rigid rocker sole (Fig. 26.13). The extra space is necessary to content a bigger foot because of the edema and of the

Fig. 26.11 StabilD: offloading device

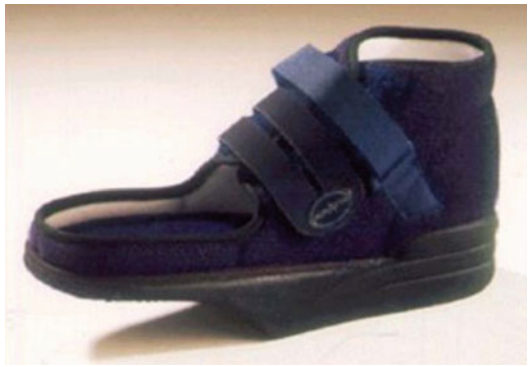

Fig. 26.12 Talus shoe: it enables the unloading of a forefoot ulcer because the patients walk by loading only the rear foot

Fig. 26.13 Temporary footwear with extra volume and rigid rocker sole

infection that can be present, an insert that can be grossly molded to form a depression in which the ulcerated area can be accommodated and unloaded, and bandages that can be different in volume according to the needs of the ulcer. The rigid sole guarantees the immobilization of the metatarsal–phalangeal joint and a reduced load at the level of metatarsal heads [36]. The foot ulcer unloading given by temporary footwear is not equivalent to that of total contact cast or walking casts [26]; however, this kind of device may have other advantages such as its wider usability because of the absence of adverse effects, a better acceptance and therefore better compliance by the patients because of their feeling of a quite normal lifestyle with the possibility of having little walks, of driving the car, while taking care of their foot ulcers.

Relevant Literature Update and Innovation

Relevant issues raised in the most recent literature are here below briefly reported and discussed, which deal with several aspects of the care of the diabetic foot through footwear and plantar orthoses.

Shear Stress and Plantar Pressures [20]

Recent literature greatly addressed the concept that shear stress, as well as compressive forces, plays a critical role in the development of plantar ulcers and deserves equal attention. Studies that have tried to associate only pressures with ulcer occurrence, in fact, did not yield promising outcomes [37]. They found that elevated pressure levels do increase ulceration risk, but only a relatively low correlation has been found in these studies between the maximal pressure sites and the prospective ulcer sites. Lavery et al. encourage to study shear stress deeply, also considering that during a single stance the same local area under the foot, and in particular the forefoot area, can experience stresses in opposite directions due to braking forces in the contact phase and propulsive forces in the push-off phase. They also suggest focusing on two specific parameters: the peak-to-peak shear and the shear-time integral.

The main problem with the management of shear stress is that it is hardly measurable, thus an objective evaluation of the effectiveness of the proposed solutions is still far to be reached especially in clinical routine.

Some authors [38–40] give the suggestion that peak pressures should be reduced as well as duration of maximum pressure (i.e., pressure time integral) and shear stress. First key-point to reduce shear is the choice of appropriate shoe size and shape in order to minimize damages due to friction. The second, relevant key-point which is currently suggested and under investigation is the criterion to further reduce friction by lubricating the surfaces moving against one another and by

keeping the foot dry; this can be obtained by using shear-reducing socks with low coefficient of friction (COF) instead of traditional cotton socks which have relatively high COF. As ex example, the Dual-Layer Performance socks by Sole [41] consist of a mixture of Tactel, Lycra and Coolmax fabrics and result in a comfortable product which allows breathability and whose inner layer becomes solid with the foot and slides against the outer layer to reduce friction on the foot.

Friction reduction can also be obtained by using shear-reducing material on the interior of the shoe or on the surface of a foot orthosis. A good example is represented by a Teflon material called Shear Ban (Tamarack Habilitation Technologies Inc, MN, USA) which is a self-adhesive, heat-moldable material made to adhere to most surfaces.

Foot Orthoses (Updated Criteria)

Custom therapeutic insoles tailored to contours of the barefoot pressure distribution and shape of a patient's foot can reduce plantar pressures in the metatarsal head region to a greater extent than conventional custom insoles [42]. The greater offloading is obtained by a greater transfer of load to the mid foot without additional loading of the other forefoot structures. Obviously, this indication is not appropriate in the treatment of a Charcot's foot.

Main features in the design and construction of foot orthoses for a diabetic neuropathic foot have been helpfully summarized in the 2010 review by Janisse et al. [20] and are briefly reported and discussed here below:

- Foot orthoses, in any diabetic neuropathic case, need to be custom-made, and aim to improve pressure distribution via total contact between orthosis and foot. In general, they should be made of a soft, conformable, cushioned top layer in conjunction with a firmer, supportive base layer. The contours of the plantar surface of the foot should be filled with material and then planned flat on the bottom so that when the patient stands on the orthosis the entire plantar surface of the foot is weight bearing.
- Most used material for top layer is Plastazote, which is a moldable, static dissipative, nitrogen-charged, closed-cell, cross-linked polyethylene foam. Unfortunately, its lifecycle is relatively short; usually, it is supported by a thin layer of polyurethane foam or EVA. The base layer must be supportive and shock absorbing for an insensate foot, and easily adjustable; thus, rigid thermoplastic material or carbon composite should be avoided, while suitable materials are EVA or cork composite with EVA, thermoplastic, latex rubber, or fiberglass. These materials—Shore A durometer in between 50 and 60—are also interesting since they can be used in conjunction with CAD-CAM systems for the construction of foot orthoses under machine controlled conditions.
- In the preparation of orthoses, semi-weight bearing mold should be used rather than off-loaded or full weight-bearing molds, since it has been showed that this solution delivers products which best address the foot needs during standing and walking.
- Proper pads may be added to the above custom-made orthoses proximal to specific areas which ask for further pressure reduction.

With regards to the very last point of the above list—the addition of "proper pads"—a very interesting study has been published in 2008 by Actis [43] which proposes the use of custom made insoles with a certain number of plugs of softer material inserted in the forefoot area to further reduce its loading. The study, based on the use of finite element models (FEMs) and on the statement that TCIs can reduce peak plantar pressures up to more than 40% under the metatarsal heads compared to the therapeutic footwear alone, deals with the design of TCIs with special "solutions" improving the technique of the added pads. The study showed that customized inserts with softer plugs distributed throughout the regions of high plantar pressure reduced the peak plantar pressure more than the TCI can do alone. The solution is an improvement with respect to the use of different plug designs since it does not cause edge effects and provides a greater degree of flexibility for customizing orthotic devices than current practice allows. The study was focused on a

Plastazote Shore 35 TCI of 1.27 cm height, heightened to include the medial arch support and made to be used with standard therapeutic shoes (SoleTech shoes style E3010) [44]. Seven plugs made of Poron—4 mm in diameter—were inserted into the forefoot area of the TCI, spaced 1 mm, and penetrated 7 mm into the TCI. This solution seems to be preferable to the single plug design which showed an undesirable secondary pressure peak 20 mm distally from the center of the metatarsal head at the end of the plug.

Foot Structure and Footwear Prescription

A very well done review dealing with the issues of foot treatment and footwear prescription in case of diabetic foot at risk of ulceration was delivered by Bus et al. in 2008 [4]. In the paper, a thorough investigation is conducted to better understand why, despite the wide prescription of custom footwear especially after ulcer healing, in order to redistribute and reduce plantar foot pressures and to prevent ulcer recurrence, the available evidence for the effectiveness of this solution is not yet strong. As possible factors, the author indicates: the lack of standardized or systematic approach in footwear prescription and evaluation; significant variability across patients in the offloading effect of different footwear interventions. Also the different scenarios of the foot and ankle alterations in both structure and function may contribute to render the efficacy of the prescription more variable. With respect to this last issue, most common abnormalities to deal with when prescribing footwear are: callus formation, prominent metatarsal heads, claw/hammer toe deformity, hallux valgus, and limited joint mobility; in some cases, even though the prevalence is low, mid foot deformity is present due to Charcot neuro-osteoarthropathy. Further frequent abnormalities obtained by foot imaging are plantar foot muscle atrophy, distal displacement of the protective metatarsal heads fat pads; reduction in submetatarsal head fat tissue thickness; increase of subphalangeal fat tissue thickness; plantar fascia thickening.

Generally speaking, a proper footwear prescription should deal with redistribution and reduction of pressures under the foot and reduction/avoiding of mechanical stress on the dorsum. This may involve the fabrication of accommodative insoles that follow the contours of the plantar foot surface (total contact) and also the use of fully customized (therapeutic or orthopedic) shoes with eventual corrective elements, such as arch supports, metatarsal pads and bars, or specific outsole configurations. Also following these indications, keeping ulcers healed seems to be a difficult task, the reported annual ulcer recurrence rate varying between 8 and 59% [45].

Improvement in the outcome of footwear prevention program might come, as suggested by Bus, from a more systematic approach to footwear prescription. The first systematic approach—the pyramid approach—was proposed in 2001 by Cavanagh et al. [46]. Basically, the "pyramid" is formed by: (1) patients without foot deformity and a relatively low activity level, who may be recommended to use proper athletic shoes; (2) patients with increasing degrees of foot deformity and activity level, who need more protective, biomechanically effective and eventually more customized solution; and (3) patients with severe deformities and an active life style, who need fully customized solution. Again in 2001, a footwear construction algorithm was delivered by Dahmen et al. [39] which is mainly based on medical condition and type of deformity. Main features of the algorithm are insole design, shoe height, rigidity of the outsole, and pivot point location. Bus found no scientific evidence related to the above approaches.

As the literature shows [4], current knowledge on the efficacy of footwear design features is based mainly on foot pressure studies, which basically proved that:

- The rocker outsole is the most effective design feature in therapeutic footwear (reduction up to 50% of forefoot peak pressures with respect to standard shoes).
- There is a great relevance of the pivot point location.
- Custom-made insoles are more effective in reducing peak pressures at the sites of previous

ulceration with respect to flat cushioning insoles; pressure relief was found up to 39% for customized insoles made with a medial arch support and a metatarsal pad to transfer proximally to the mid foot part of the load.
- More corrective than accommodative specific design features can effectively reduce pressure at high-risk locations.
- There is a great variability in patient's benefit.
- The offloading effect of a custom footwear intervention is difficult to predict for an individual diabetic patient and greatly depends on the technician responsible for footwear manufacture.

In 2009, a proposal was reported in the literature [47] to objectively quantify efficacy of footwear intervention by using a proper indicator: the authors suggest using a target of 200 kPa of in-shoe peak pressure as the indicator of efficacy of the individual footwear intervention. This proposal is extremely interesting and may become useful indeed. However, it is mandatory to keep in mind that, when efficacy has to be proved through an objective measurement, this needs to be standardized and assessed as for accuracy of the measurement instrumentation and correctness, appropriateness, and comparability of the measurement protocol. In case, these essential requirements are not fulfilled, the risk of wrong conclusions and consequent wrong therapeutic intervention indeed becomes very high! [48]. Bus et al. [4] strongly supports the idea of an objective evaluation as obtained through an accurate in-shoe plantar pressure analysis, and encourages the establishment of evidence-based guidelines for proper footwear prescription and evaluation in patients with diabetes which currently do not exist, and currently prescription success is still evaluated on the basis of whether the patient remains free from injury. Bus et al. [49] also indicated the solution of a footwear optimization based on successive footwear assessment and modifications, with the final target to reduce peak pressures below 200 kPa or 25% compared to baseline.

Recent papers investigated evidence of footwear prescription effectiveness not only as an isolated treatment, but also in conjunction with education programs as indicated by the International Consensus on Diabetic Foot [50]. Among these, a well-designed 2-year study was applied and the outcomes published [51]; main finding was that although the proposed program lowered recurrence rates and increased the duration of ulcer-free survival, it was unable to prevent occurrence and recurrence of neuropathic ulcers due to diabetes. (In the study, however, the footwear was not a proper custom-made footwear: two models were chosen of therapeutic shoes, their width selected on the basis of the distance between first and fifth metatarsal heads, and their size on the basis of the maximum longitudinal length of the foot.)

The Relevance of Proper Shoe Fitting

Twenty percent of ulceration in patients with diabetes is a result of ill-fitting footwear [52, 53], partly due to the fact that when purchasing footwear, patients may be strongly influenced by fashion and financial resources. Recent studies proved that, despite a correct shoe fitting is mandatory for the success of a footwear therapeutic intervention in diabetic patients both in primary and secondary prevention, a lot of patients still wear ill-fitting shoes. Furthermore, if neuropathy coexists with peripheral vascular disease, tight shoes may be even more problematic because it may induce lesions on the area with localized high pression.

In a paper by Harrison et al. [54], a study was described which included 100 diabetic patients: 1/3 of them resulted to be wearing the correct shoe on either foot while sitting or standing; however, only 24% of patients were wearing shoes that were of the correct length and width for both feet while sitting and 20% upon standing. In most cases, the ill-fitted shoes were too narrow, reasonably because at shoe selection the simple below indications had not been followed: (a) shoes for diabetics should be wide enough to accommodate the first metatarsophalangeal joint; (b) shoes should be fitted while weight bearing: foot size, in fact, usually increases from sitting to standing, on average, 0.3–0.4 size, but can go up to 1–1.5

size; (c) the location of the widest part of the shoe should be checked allowing extra room at the toe box, adequate room should be left across the ball of the foot and a good and stable fit should be made around the heel; and (d) foot size should be accurately measured. With respect to the last point, the authors suggest that "shoe should be considered of an incorrect length when the difference between foot length and shoe length (in shoe size) is more than half a size difference. A shoe should be considered of an incorrect width when the difference between foot and shoe width is greater than one width size (0.7 cm)".

According to the authors, main reason for selecting wrong shoe size are: (a) adults do not get their feet measured on a regular basis: foot size should always be checked properly prior to shoe purchase; (b) fashion issues may also be a factor; (c) shoe sizes among shoe manufacturers are not standardized; and (d) many manufacturers do not make half sizes and shoes of varying widths: often patients have to buy longer shoes to get the width fitting they require to accommodate their feet.

A paper from Parnes [55] underlines that, besides the already reported drawbacks of ill-fitting shoes, the increased risk of fall should be taken into account, too.

New Ideas and Suggestions for Footwear Treatment

In a paper from Tazi and Debure [56], a novel custom-made shoe is proposed: the innovation is represented by the very thick multiple layer total contact sole (mean thickness 25 mm for a forefoot deformity and 40 mm for a mid foot deformity. No studies have been found in the literature up to now dealing with the wide clinical application of this proposal.

Dabiri et al. [57] proposed an electronic orthotic shoe: a prototype of a wireless electronic orthotics composed of lightweight embedded systems and noninvasive sensors was constructed to monitor foot motion and pressure distribution. The system allows the online feedback mechanism and the eventual alert messaging to patient and caregiver. No further evidence has been found in the literature dealing with the clinical application of this interesting idea.

Some proposals are instead coming from the market which should be well understood by professionals and patients dealing with diabetic foot complications. Basically, they consist of walking or running comfortable shoes or sport shoes whose main working principle is the onset of little unbalance so as to increase muscle activation to better control standing and walking. They claim they contribute to improve muscular tone, joint mobility, posture, and so on. We are not here discussing the extent of these effects on healthy subjects: we are most worried about the eventual destabilizing effects on diabetic patients who are not well informed about the possible increase of risk of fall. In those solutions where a rocker sole—even though flexible—is also present, the pivot point is usually distally placed with respect to what asked by a diabetic neuropathic foot, thus the effect of the rocker to shift loading proximal to the metatarsal heads is lost.

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