1 Understanding Diabetes for Reconstruction

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1.1 Why Understanding Diabetes from the Medical Perspective Matters for Reconstruction

The prevalence of diabetes mellitus (DM) is growing at epidemic proportions worldwide [1]. Globally, approximately 463 million adults (20–79 years) are living with diabetes, and by 2045, this is expected to increase to 700 million [1].

Diabetic foot complications are one of the major complications of diabetes that lead to a significant number of hospitalizations, medical expenses, disabilities, and deaths [2]. Diabetic foot problems can occur as a result of ischemic or neuropathic ulcers, traumatic wounds, skin cracks or fissures, or other infections in the skin of the foot or nail beds (paronychia) [3]. The initiating problem, usually a minor trauma that causes cutaneous ulceration, can often be identified.

Diabetic foot complications are estimated to affect 40–60 million people with diabetes worldwide [1]. In patients with diabetes, the lifetime incidence of diabetic foot ulcers may be as high as 34% [4]. The risk of death at 5 years for a patient with diabetic foot ulcers is 2.5 times higher than that of a patient with diabetes who does not have foot ulcers [5]. More than 50% of cases of diabetic ulcers are infected, and approximately 20% of moderate or severe diabetic foot infections result in amputation [6]. Mortality after amputation related to diabetic foot problems exceeds 70% after 5 years [7].

Several risk factors such as neuropathy, vascular disease, and foot deformities can predict ulcers and amputation. Early recognition and management of risk factors are important for decreasing diabetic foot problems [4].

Neuropathy is a disease that affects the nerves, leading to impaired sensation, movement, and other health aspects depending on the nerve affected. Diabetic neuropathy is the most common complication of diabetes, with a lifetime prevalence rate of 60% [8]. Neuropathy is the most crucial risk factor underlying the development of foot ulcers. Peripheral neuropathy manifests as sensory, motor, and autonomic neuropathy [9]. Sensory neuropathy is a more frequent complaint than motor neuropathy. Sensory neuropathy presents as "glove and stocking" in the feet as hyperesthesia, hypoesthesia, or anesthesia. Motor neuropathy manifests as weakness of the foot or clawing of the toes [10]. Autonomic neuropathy presents as tachycardia when stable, orthostatic hypotension, gastric paralysis, overactive bladder, erectile dysfunction, and hypoglycemic unawareness [11, 12]. Neuropathic disturbances

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in sensory, motor, and autonomic functions result in loss of skin integrity [13].

In patients with diabetes, loss of sensation in a joint may lead to a chronic, progressive, and destructive foot deformity. Charcot arthropathy is the typical deformity. It is related to tabes dorsalis and is characterized by the slow degeneration of the neural tracts, primarily in the dorsal root ganglia of the spinal cord. The pathogenesis of this condition remains unclear, but it is likely to be multifactorial, such as a combination of mechanical and vascular factors and diabetic neuropathy [14].

Peripheral arterial disease (PAD) is an atherosclerotic occlusive disease of the lower extremity. Diabetes is a significant risk factor for PAD [15]. PAD can appear in up to 50% of patients with diabetic foot ulcers and is a risk factor for poor recovery and amputation [16]. In addition, the presence of PAD is notably related to reduced survival in the patients with diabetic foot ulcers, which are responsible for 70% mortality due to diabetes [17]. Patients with diabetes have a higher incidence of atherosclerotic occlusion of the large and medium-sized arteries, e.g., aortoiliac or femoropopliteal arteries, which causes ischemia. With digital artery disease, improper arterial blood supply and, thus, peripheral ischemia worsen foot ulcers and cause poor wound healing [6, 15]. Less arterial perfusion also causes infection, chronic impaired wound healing, and amputation [15].

The strategy for managing diabetic foot is prevention. For this, the most fundamental strategy is to control diabetes itself by optimizing glycemic control [8]. For type 1 and type 2 diabetes, glycemic control can reduce complications, as demonstrated in landmark trials (The Diabetes Control and Complications Trial (DCCT) [18] and UK Prospective Diabetes Study (UKPDS) [19]). The DCCT demonstrated that intensive glucose control was associated with improved long-term outcomes [20]. Follow-up for more than 10 years after active treatment in the DCCT showed there were less microvascular complications in the group that received intensive treatment [21]. The UKPDS demonstrated that intensive glycemic control significantly reduced microvascular complications in patients with type 2 diabetes [19]. Long-term follow-up of the UKPDS groups showed lasting effects of early glycemic control on microvascular complications [22].

The major factor that leads to the development of a diabetic ulcer is neuropathy. Glycemic control could contribute to reducing the incidence of neuropathy, but it can not completely prevent it, as shown in the UKPDS [19, 22]. Patients with decreased sensation in the feet due to neuropathy can benefit from several strategies to develop an overall plan for preventive management. Early recognition of new lesions in a patient with a diabetic foot ulcer is critically important for reducing the risk of complications. Diabetic foot ulcers are often accompanied with infection and PAD, resulting in complex wound problems [6, 16]. Thus, moderate or severe ulcers lead to amputation [6], which reduces the quality of life and increases mortality [7]. Reconstruction has been developed and used for the treatment of diabetic foot ulcers and reduction of the number of amputations [23]. Despite the comprehensive strategy for prevention, ulceration of the foot may occur. In this situation, surgical reconstruction of the skin may be necessary for treatment. Skin reconstruction, such as skin grafts or local flaps, can be used for discrete areas that do not heal easily [24]. The greatest advantage of reconstruction is to provide the opportunity for bipedal ambulation by salvaging the limb. However, assessment of vascularity should be made before reconstruction to evaluate the likelihood of healing [25]. If the vascularity to the foot is poor, then reconstruction may fail.

1.2 Medical Diabetes

1.2.1 Definition

Diabetes mellitus is a chronic metabolic disorder of glucose homeostasis leading to hyperglycemia. It is caused by an absolute deficiency of insulin (type 1 DM) or by a relative deficiency of

insulin combined with a decrease in insulin sensitivity, known as insulin resistance (type 2 DM). Insulin, a peptide hormone, is produced by the pancreatic β-islet cells and plays a crucial role in regulating blood glucose levels. Insulin allows cells to absorb glucose for use as fuel or storage and suppresses glucose formation by the liver. It also stimulates protein synthesis and inhibits the breakdown of fat.

Type 1 DM is autoimmune process that destroys pancreatic β-islet cells and is triggered by unknown precipitating events such as a viral illness in a susceptible host. It usually leads to absolute insulin deficiency. It is not a lifestyle-related disease and tends to occur in children and younger adults.

Type 2 DM is caused by progressive loss of appropriate β-cell insulin secretion and insulin resistance. It tends to occur in patients with a strong family history and those with environmental factors such as sedentary lifestyles or obesity. Therefore, type 2 DM generally occurs in older and overweight adults, and nowadays, it is also common in obese children and adolescents. Worldwide, 463 million people, or 9.3% of adults, have diabetes, and this number in growing exponentially. By 2045, 700 million people or 10.9% of adults are expected to have diabetes [1]. Half of those with diabetes (50.1%) do not know that they have diabetes [1].

Many asymptomatic people have "prediabetes," either impaired fasting glycemia (IFG) or impaired glucose tolerance (IGT). Prediabetes means that glucose levels do not meet the criteria for diabetes but are higher than normal [18]. IFG is defined as fasting plasma glucose (FPG) levels between 100 and 125 mg/dL, and IGT is defined as a 2-h plasma glucose during 75 g oral glucose tolerance test (OGTT) levels between 140 and 199 mg/dL [26]. Prediabetes is a risk factor for diabetes, cardiovascular disease, obesity, dyslipidemia, and hypertension [26]. The global incidence of IGT is estimated to be 7.5% (374 million) in 2019 and is expected to increase to 8.6% (548 million) by 2045 [1].

1.2.2 Diagnosis

Hyperglycemia is measured through laboratory findings of elevated plasma glucose levels, either fasting, random, or OGTT (Table 1.1). Diagnosis is made based on the results of two abnormal tests from the same sample or in two separate test samples. In the presence of typical symptoms, only one elevated plasma glucose result is required.

Clinical symptoms of hyperglycemia are polyuria, nocturia, dehydration, weight loss, tiredness, and blurred vision. In Type 1 DM, these symptoms may be acute at onset, and the patient may become ill with diabetic ketoacidosis. However, type 2 DM shows a more insidious onset, and symptoms usually go unnoticed for many years.

1.3 Complications of Diabetes Mellitus

Diabetes mellitus is a major cause of morbidity and mortality and is sixth-leading cause of death in the USA. It is also a major underlying cause of coronary heart disease and cerebrovascular disease. In many studies, the mortality rate of indi-

Table 1.1 Diagnosis of diabetes mellitus

FPG ≥ 126 mg/dL[a]
OR
2-h PG ≥ 200 mg/dL during OGTT[b]
OR
A1C ≥ 6.5%
OR
Random plasma glucose ≥200 mg/dL (in a patient with classic symptoms of hyperglycemia or a hyperglycemic crisis)

FPG fasting plasma glucose, *OGTT* oral glucose tolerance test, *2-h PG* 2-h plasma glucose

[a]Fasting is defined as no caloric intake for at least 8 h

[b]The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water

viduals with DM is two times higher than that of individuals without diabetes.

1.3.1 Acute Complications of Diabetes Mellitus

DM leads to infection, caused by either bacteria and fungi, and may result in hyperglycemic crises such as diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome. Treatment of diabetes with oral agents or injections may cause complications such as hypoglycemia (Table 1.2).

1.3.2 Chronic Complications of Diabetes Mellitus

Diabetes affects both small vessels (microvascular complications) and large vessels (macrovascular complications). Microvascular complications include diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy (Table 1.3). Macrovascular complications include coronary heart disease, cerebrovascular disease, and PAD (Table 1.4).

Among the many complications of diabetes, neuropathy and PAD are most likely to affect the incidence of diabetic foot and reconstruction outcomes. Diabetic neuropathies are a heterogeneous group of disorders with diverse clinical manifestations. Diabetic neuropathy is the most common complication in diabetes, with a lifetime prevalence rate of 60% [8]. Up to 50% of cases of diabetic peripheral neuropathy may be symptomatic. The most common manifestations of neuropathy are diabetic peripheral neuropathies such as distal symmetric sensorimotor polyneuropathy and autonomic neuropathy [27]. Distal symmetric sensorimotor polyneuropathy is the most common type of diabetic neuropathy and is often considered synonymous with the term diabetic neuropathy. It is characterized by a progressive loss of distal sensation correlating with the loss of sensory axons, followed by motor weakness and motor axonal loss. Classic "stocking-glove" sensory loss is typical in this disorder [8]. Diabetic autonomic neuropathy is a common complication of diabetes. It is diagnosed by exclusion and may be unnoticed because of multiorgan involvement and its insidious onset. However, it can lead to severe dysfunction of a single organ, such as postural hypotension, gastroparesis, and genitourinary disturbance [28].

Table 1.2 Acute complications of diabetes mellitus

Diabetic ketoacidosis	Hyperglycemic crisis with a high anion gap due to acidic substances called ketones
Hyperglycemic hyperosmolar syndrome	Hyperglycemic crisis with increased serum osmolarity
Hypoglycemia	Overdose of diabetes medication relative to food intake

Table 1.3 Microvascular vascular complications of diabetes mellitus

Disease	Clinical and laboratory features
Diabetic retinopathy	
Non-proliferative	Microaneurysms, exudates, macular edema
Proliferative	Vulnerable new vessels, vitreous hemorrhage, retinal detachment
Diabetic nephropathy	Microalbuminuria: Urine Alb/Cr ≥ 30 and <300 mg/g or 24 h urine albumin ≥30 and <300 mg/day
	Macroalbuminuria: Urine protein/Cr ≥ 0.3 mg/g or 24 h urine protein ≥ 0.3 g/day
	End-stage chronic kidney disease
Diabetic neuropathy	Motor: Abnormal posture or feet deformities, e.g., clawed toes
	Sensory: Reduction in vibration, monofilament, touch sensation, and proprioception
	Autonomic: Postural hypotension, gastroparesis, diarrhea, neurogenic bladder, impotence, dry feet

Table 1.4 Macrovascular vascular complications of diabetes mellitus

Disease	Clinical and laboratory features
Coronary heart disease	Angina pectoris, myocardial infarction (MI), heart failure
Cerebrovascular disease	Stroke, hemorrhage
Peripheral arterial disease	Intermittent claudication, rest pain, ulcer, gangrene

PAD, defined as atherosclerosis in the arteries of the lower extremities, is also a strong risk factor for diabetic foot problems [29]. Moreover, PAD causes significant long-term disability in patients with diabetes [30]. PAD affects approximately one-third of those with comorbid DM [30]. The prevalence of PAD may be underestimated in patients with diabetes owing to the asymptomatic nature of less severe PAD and the often concomitant diabetic neuropathy [30]. The clinical manifestations of PAD, which include claudication, rest pain, ulceration, and gangrene, are predominantly caused by progressive luminal stenosis or occlusion.

1.4 Treatment of Diabetes Mellitus

Both Type 1 and Type 2 DM require lifestyle modifications, i.e., regular exercise for a duration of 150 min/week [31], and regular, calorie-regulated meals with less simple sugars, and more complex carbohydrates, fiber, and low glycemic index foods [32]. Diabetes patients should stop smoking cigarettes and consume a moderate amount of alcohol to reduce cardiovascular risks.

1.4.1 Type 1 Diabetes Mellitus

Type 1 DM patients require insulin to live. An intensive insulin regimen, multiple daily injections (MDI), or an insulin pump are preferred for better glycemic control and fewer microvascular complications [18]. Traditionally, short-acting soluble insulin, such as Humulin R, is administered with intermediate-acting NPH insulin, such as Humulin N. Nowadays, insulin analogs are available, which are more convenient to use with fewer hypoglycemic episodes. For example, rapid-acting insulin analogs such as Insulin Lispro, Glulisine, Aspart, or faster Aspart can be injected immediately before and after eating each meal. Longer acting insulin analogs such as Glargine, Detemir, or Degludec can help provide peakless basal insulin, leading to fewer hypoglycemic episodes (Table 1.5).

Table 1.5 Type of insulin

Insulin	Compound
Rapid-acting	Lispro
	Glulisine
	Aspart
	Inhaled insulin
Short-acting	Human regular
Intermediate-acting	Human NPH
Concentrated human regular insulin	U-500 human regular insulin
Long-acting	Glargine
	Detemir
	Degludec
Premixed insulin products	NPH/regular 70/30
	NPH/Lispro 50/50
	NPH/Lispro 75/25
	NPH/Aspart 70/30

1.4.2 Type 2 Diabetes Mellitus

Various oral hypoglycemic agents are available with different mechanisms of action and effects (Table 1.6). Metformin has been initially recommended for diabetes patients for many years. Sulfonylureas have also been regularly used for many years. Thiazolidinediones (or glitazones) have been shown to improve insulin sensitivity. More recently, incretin mimetics, dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), which act by increasing the active level of the hormone glucagon-like peptide-1 (GLP-1) secreted by the small intestine, are available in the form of tablets and injections, respectively. SGLT2 inhibitors inhibit renal glucose reabsorption. However, after acquiring type 2 diabetes for 10 years, many patients need insulin therapy. Initially, once-daily long-acting insulin added to oral agents may control the diabetes, but eventually, patients may need more frequent insulin injections.

Table 1.6 Type of oral hypoglycemic agents

Class	Name
Biguanide	Metformin
Sulfonylureas (2nd generation)	Glyburide, Glibornuride, Gliclazide, Glipizide, Gliquidone, Glisoxepide, Glyclopyramide, Glimepiride
Meglitinides (glinides)	Repaglinide, Nateglinide, Mitiglinide
Glucosidase inhibitors	Acarbose, Miglitol, Voglibose
Thiazolidinediones	Pioglitazone, Rosiglitazone, Lobeglitazone
DPP-4 inhibitors	Sitagliptin, Saxagliptin, Linagliptin, Alogliptin, Vildagliptin, Gemigliptin, Teneligliptin, Anagliptin, Evogliptin, Trelagliptin, Omarigliptin, Gosogliptin
GLP-1 receptor agonists	Exenatide, Extended-release exenatide, Liraglutide, Albiglutide, Dulaglutide, Lixisenatide, Semaglutide
SGLT2 inhibitors	Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin, Ipragliflozin, Luseogliflozin, Remogliflozin etabonate, Tofogliflozin

1.5 Management of Diabetes Complications

1.5.1 Glycemic Control

The UKPDS [19] and Kumamoto Study [33] demonstrated that intensive glycemic control significantly reduced rates of microvascular complications in patients with short-duration type 2 diabetes. Long-term follow-up of the UKPDS showed enduring effects of early glycemic control on most microvascular complications [22]. Thus, achieving A1C targets of 7% has been observed to decrease microvascular complications of type 1 and type 2 diabetes when instituted early in the course of disease [34]. Therefore, treatment for diabetes aims at tight control of glucose levels, and therefore, frequent monitoring of these parameters is essential (Table 1.7).

Among hospitalized patients, careful management of diabetes has benefits. A HbA1c test on all hospitalized patients with diabetes or hyperglycemia (blood glucose >140 mg/day) is recommended. Insulin therapy should be initiated for persistent hyperglycemia (≥180 mg/dL). Once insulin therapy is initiated, a target glucose range of 140–180 mg/dL is recommended for the majority of critically and noncritically ill patients [35, 36]. When caring for hospitalized patients with diabetes, consult with a specialized diabetes or glucose management team.

Table 1.7 Glycemic recommendations for adults with diabetes

A1C	7.0%
Preprandial capillary plasma glucose	80–130 mg/dL[a]
Peak postprandial capillary plasma glucose	180 mg/dL[a]

[a]More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on the duration of diabetes, age/life expectancy, comorbidities, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations

1.5.2 Management of Peripheral Neuropathy and PAD

Symptomatic diabetic neuropathy is generally not reversible, and management aims to slow further progression and prevent complications such as diabetic foot ulcers. Optimal glycemic control has an important role in slowing the progression of neuropathy [28]. In patients with neuropathy, foot care is essential to help reduce the risk of complications. In addition, symptomatic therapies for neuropathic pain are important for management. Pain medications are not useful for nonpainful symptoms of neuropathy, such as numbness. Pharmacotherapy options for painful diabetic neuropathy include several antidepressants (e.g., duloxetine, venlafaxine, amitriptyline, and other tricyclic drugs) and gabapentinoid antiepileptic drugs (pregabalin, gabapentin) [37]. Among these, pregabalin, duloxetine, and gabapentin are recommended as initial pharmacologic treatments for neuropathic pain in diabetes [8].

The management of patients with diabetes and PAD is focused on relieving symptoms and

lowering the risk of cardiovascular disease progression and complications. Smoking cessation, lipid-lowering therapy, antihypertensive therapy, glycemic control, diet, and exercise are recommended to reduce the risk of future cardiovascular events, including limb-related events [38, 39]. Long-term antithrombotic therapy using aspirin (75–100 mg/day) or clopidogrel (75 mg/day) is recommended for all diabetes patients with PAD to reduce the risk of overall cardiovascular events and death [40, 41]. Unless there is a clear indication, dual antiplatelet therapy is not routinely recommended for patients with DM and PAD [42]. Patients with DM and chronic limb-threatening ischemia may require revascularization procedures.

1.6 Significance of Multidisciplinary Care

Care for patients with diabetic foot problems is complicated from asymptomatic to critically ischemic limb, which needs amputation. This complexity of diabetic foot is due to a series of comorbidities, including diabetes, vascular disease, and neuropathy that exceed the boundaries of usual medical or surgical care. Of these comorbidities, the treatment must begin with strict glycemic control and nutritional support while managing the wound and infection [43]. With managing these systemic factors, peripheral vascular diseases have to be reviewed, and play a crucial role to improve circulation for further reconstruction.

Patients with diabetic foot problems have poor glycemic control and thus need the comprehensive treatment from an endocrinologist. An infectious disease specialist is also required because patients with diabetic foot problems often have severe infections. Moreover, because many patients have peripheral vascular disease with poor blood supply, an experienced cardiologist and a vascular surgeon are also needed to improve the limb salvage rate. Orthopedic and plastic surgeons perform debridement of the wound or remove the infected soft tissue and bone. Plastic and reconstructive surgery helps the restoration of the form and function of the foot. Specialized wound podiatrists and nurses also play crucial roles in managing diabetic foot problems. To effectively manage these complicated aspects in patients with diabetic foot problems, multidisciplinary team approach would be helpful.

A multidisciplinary diabetic foot team has been working at Asan Medical Center (AMC) since 2015. This team is mainly composed of endocrinologists, plastic surgeons, orthopedic surgeons, cardiologists (specialized for peripheral artery intervention), and specialized nurses. In AMC, if patients with diabetic foot problem need hospitalization, whatever specialist evaluated the patients, they were admitted to endocrinology department. Patients with diabetic foot problem often have various medical problems such as poor glycemic control, chronic kidney disease, or cardiovascular disease. Therefore, after the patients were hospitalized to endocrinology department, conservative treatments including glycemic control, antibiotics use, and fluid & electrolyte imbalance correction were performed. Depending on the patient's condition, plastic surgeon, orthopedic surgeon, and cardiologist conducted debridement, amputation, and angioplasty, respectively. The multidisciplinary diabetic foot team in AMC had a conference once a week to discuss and decide the patients' treatment directions.

Moreover, when patients with diabetic foot problem who need emergent surgical treatment came to emergency room, plastic or orthopedic surgeons perform emergency debridement within 24 h, which contribute to stabilization of the patients' condition. After hospitalization, the patient is continuously treated with team approach as described above.

This kind of multidisciplinary team approach is important to limit the spread of acute infection and lead to limb salvage. This team approach provides efficiency because time is not wasted for waiting specific department's consultations. The team approach provides the link between the departments to work closely together when making challenging medical and surgical decisions.

The comorbidities of diabetic foot result in poor ulcer healing and eventually increase the risk

of major amputation [44]. A multidisciplinary team approach for individuals with foot ulcers and high-risk feet is important to optimally deal with these comorbidities to reduce major amputations [8]. Several systemic reviews evaluated the impact of multidisciplinary team care on diabetic foot disease outcomes [32, 45, 46]. In these studies, multidisciplinary teams were related to significant decreases in major (above-ankle) amputations for patients with diabetic foot problems. Multidisciplinary team care is an effective strategy for the highest risk patients, especially those with severe ulcers requiring hospitalization and underlying peripheral vascular disease. This is consistent with expert opinion guidelines suggesting a comprehensive approach to care [47].

Therefore, it is important to form a multidisciplinary team comprising an endocrinologist, an infectious disease specialist, a cardiologist, an orthopedic surgeon, a plastic surgeon, a vascular surgeon, a podiatrist, specialized nurses, and other allied health professionals to handle various problems in patients with diabetes. Multidisciplinary teams, composed of physicians who are able to control glycemic levels, manage peripheral vascular disease, properly care for infections, and provide localized wound management, were related to a decreased risk of major amputation for patients with severe diabetic foot disease.

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