Chapter 39
Diabetes in the Elderly

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Diabetes Mellitus

Diabetes mellitus is a metabolic disease characterized by hyperglycemia, resulting from a relative or absolute deficiency of insulin [1]. Type 2 diabetes is the most common chronic metabolic disease in the elderly, affecting ~30 million individuals 65 years of age or older in developed countries [2]. It is estimated that approximately 40% of people over the age of 65 have diabetes or impaired glucose tolerance (IGT) [3, 4] (Fig. 39.1).

The exact pathogenesis of the development of diabetes in the elderly remains unknown; however, epidemiological studies have shown that the transition from the normal state to overt type 2 diabetes in the elderly is typically characterized by deterioration in glucose tolerance [5, 6], which is due to relative or absolute insulinopenia. One current hypothesis holds that muscle insulin resistance develops with aging and leads to increased demand for insulin secretion by the beta cells in order to compensate for the insulin resistance. This continuous high demand for insulin secretion may over time cause beta-cell failure and thereby lead to overt type 2 diabetes. Several studies in the elderly have documented insulin resistance, independent on body weight, and found that insulin concentrations are two- to threefold increase in response to a standard oral glucose tolerance test (OGTT) [7]. The reason for muscle insulin resistance as a consequence of aging is still unclear. However, there is now strong cross-sectional evidence that insulin resistance in muscle can be attributed to accumulation of lipids (specific fatty acid metabolites such as diacylglycerol), which specifically blocks insulin signaling and thereby cause tissue-specific insulin resistance [8–12]. Application of magnetic resonance spectroscopy (MRS) studies to directly measure intramyocellular lipid content (IMCL) in muscle of healthy, normal weight, sedentary older people has shown that the IMCL content is ~twofold higher in the older individuals when compared with young matched for body mass index and activity [7], suggesting a similar relation between increased IMCL and muscle insulin resistance in older as in young individuals [12]. This lipid accumulation in the muscle cells is likely caused by imbalance between delivery of fatty acids to the muscle call and the rate of oxidation within the cell. In support of this, MRS studies of mitochondrial ATP synthesis and basal rates of substrate oxidation via the tricarboxylic acid (TCA) cycle in vivo in young and elderly subjects have shown that both sides of mitochondrial function are reduced by ~40% in the elderly when compared with the young, suggesting that oxidation of lipids within the muscle is reduced in normal aging and thereby may be contributing to the build-up of lipids inside the muscle cell [7] (Fig. 39.2). Other factors may be involved in causing insulin resistance such as a systemic low-grade inflammation and the release of proinflammatory factors (adipocytokines) from adipose tissue such as adiponectin, IL-6, TNF-alpha, RBP-4, and other inflammatory factors, which are elevated in obesity and in type 2 diabetes [13]. These factors are not likely to be part of the early development of muscle-specific insulin resistance and no abnormalities in any of the adipocytokines have been found in healthy, normal weight, older individuals [7]. It seems likely that increases in adipose tissue mass in obesity and type 2 diabetes may contribute to chronic inflammation and proinflammatory states by increasing the recruitment of macrophages, which in turn, act in a feed forward mechanism to induce the release of proinflammatory cytokines that may contribute to systemic insulin resistance [14].

In this context, no signs of systemic inflammation or elevation of circulating adipocytokines have been consistently found in lean, young, healthy, insulin resistant offspring of parents with type 2 diabetes, a group that has muscle-specific insulin resistance [9, 15, 16], strongly suggesting that inflammation is not a primary factor in the early development of insulin resistance in muscle [15].

The link between muscle insulin resistance and the progression to overt type 2 diabetes is dependent on relative

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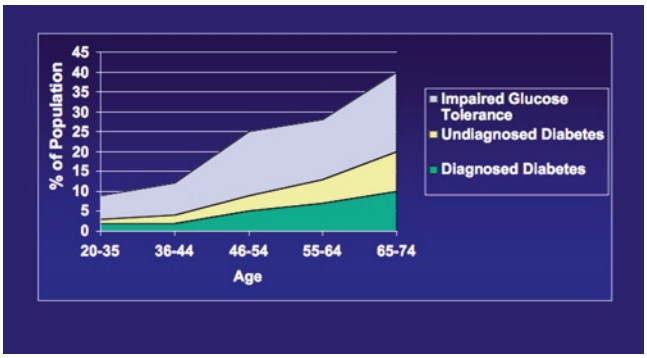

Figure 39.1 Prevalence of diabetes and glucose intolerance (reprinted with permission from Harris [4]).

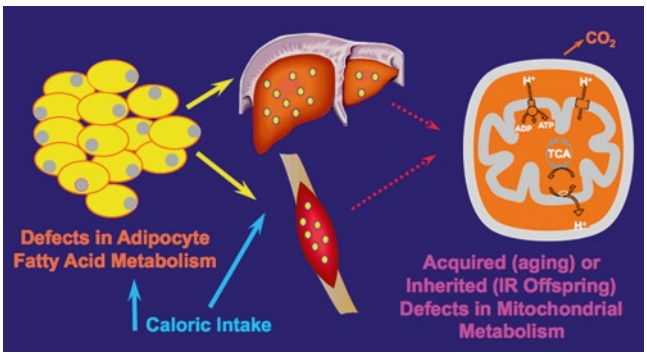

Figure 39.2 The road to insulin resistance.

Table 39.1 2003 American Diabetes Association diagnostic criteria for diabetes mellitus

Diabetes mellitus
A random serum glucose level ≥200 mg/dL plus classic diabetes symptoms
Fasting glucose level ≥126 mg/dL
Glucose level ≥200 mg/dL at 2 h during a standard OGTT
Impaired glucose tolerance (IGT)
Glucose level ≥140 mg/dL and <200 mg/dL at 2 h during a standard OGTT
Impaired fasting glucose (IFG)
Fasting glucose ≥110 and <126 mg/dL

or actual defects in pancreatic beta-cell function such that insulin secretion is insufficient for the appropriate lowering of postprandial blood glucose. Since pancreatic insulin secretion is a highly energy requiring process, it is currently speculated that reductions in beta-cell mitochondrial function could explain the development of defects in insulin secretion in the elderly and thus explain the high prevalence of diabetes in the elderly [7, 17].

The diagnosis of type 2 diabetes mellitus in young and elderly is similar as outlined by The Diabetes Expert Committee of the American Diabetes Association in 2003 (Table 39.1). The diagnosis is based on meeting one of three criteria: a random plasma glucose of ≥200 mg/dL confirmed on a subsequent day by a fasting plasma glucose (FPG) level of ≥126 mg/dL, a 2 h plasma glucose of >200 mg/dL using the standardized OGTT (75 g of anhydrous glucose dissolved in water), or a random plasma glucose of ≥200 mg/dL with associated symptoms of polyuria, polydipsia, and unexplained weight loss [1]. The guidelines also distinguish a classification of altered glucose metabolism called impaired fasting glucose (IFG) and IGT to define a category of individuals that are at increased risk of developing diabetes over time. The diagnosis of IFG is made when an individual has FPG concentrations >110 mg/dL but <126 mg/dL, and IGT when 2-h plasma glucose values of the OGTT are ≥140 mg/dL but <200 mg/dL [1].

The ADA recommendations for glucose control are an FPG of 70–130 mg/dL and a hemoglobin$_{A1c}$ (Hb_{A1c}) level of <7.0% in adults [18]. According to past epidemiological studies, lowering Hb_{A1c} into a normal range (i.e., <6%) is supposed to be associated with a decreased risk of diabetic complications. However, recently this has been questioned from data suggesting a potential increase in mortality with intense glucose lowering strategies in patients with type 2 diabetes and lowering of Hb_{A1c} to <6% [19]. This study was terminated early given an increase in all causes of mortality of participants (mean age 62) in the intensive therapy group [19]. It is therefore prudent for the clinician to set individualized goals for elderly patients based on history of severe hypoglycemia, cognitive function, life expectancy, and comorbid conditions [18].

Therapeutic management options in elderly individuals are similar to those of younger individuals. As in younger individuals, dietary interventions and lifestyle modifications, including weight loss (medical nutrition therapy or MNT), are the cornerstone of diabetic management [18]. Dietary recommendations suggest weight loss diets for obese individuals, including either low carbohydrate (<130 g/day) or low fat for overall calorie restriction, a diet consisting of low saturated fat (<7% of total calories), a minimum of trans fats intake, and <130 g/day of carbohydrates for all diabetic individuals [18]. An exercise program may have beneficial effects on glucose intolerance, blood pressure control, weight control, lipid profile, and cardiovascular status [3]. Physical activity improves insulin sensitivity by stimulating noninsulin-dependent muscle glucose uptake and increasing substrate oxidation by increasing mitochondrial biogenesis [20, 21] as well as it improves glucose intolerance in diabetic subjects [22]; however, this too should be individualized in elderly patients based on functional status [18].

Medical management and therapeutic options are also similar to the options available in younger individuals. Currently, a number of oral medications are available for the management of older adults with diabetes (Table 39.2). Sulfonylurea drugs are the most widely used. They act initially by increasing pancreatic insulin secretion and later enhance insulin sensitivity, probably via a postreceptor mechanism [23]. Hypoglycemia is the main side effect associated with sulfonylurea drugs.

Table 39.2 Currently available oral hypoglycemic agents

Drug	Mechanism of action
Sulfonylureas	Enhances insulin secretion
Second generation	
Glimepiride	
Glipizide, sustained release	
Glyburide	
Glyburide, micronized	
Glimepiride	
α-Glucosidase inhibitor	Slows colonic carbohydrate absorption
Acarbose	
Miglitol	
Biguanide	Decreases hepatic glucose production; improves insulin sensitivity
Metformin	
Thiazolidenedione	Enhances muscle insulin sensitivity
Rosiglitazone	
Pioglitazone	
Nonsulfonylurea	Stimulates insulin secretion
Repaglinide	
Nateglinide	
DPP-4 inhibitor	Prolongs incretin activity
Sitagliptin	

Metformin works primarily by suppressing hepatic glucose production (by suppressing gluconeogenesis) and to a lesser extent by improving insulin sensitivity [24]. Metformin may result in loss of appetite and weight loss, a desirable side effect in obese diabetics. It should be avoided in persons over 80 years of age and should not be used in individuals with either renal insufficiency or heart failure.

The thiazolidinediones (TZDs) is the most recently introduced group of oral antidiabetic agents [25]. These agents function as ligands for nuclear receptor transcription factors (PPARgamma) that regulate genes involved in lipid metabolism and homeostasis. PPARgamma is preferentially expressed in adipose tissue. Activation of PPARgamma leads to adipocyte differentiation and improved insulin signaling of mature adipocytes. Although the main target for action of the TZDs is adipose tissue, their main effect in type 2 diabetes appears to be primarily by enhancing muscle insulin sensitivity [26]. This paradox may be explained by the mechanism of action of TZDs, which are fat cell proliferators and thus by creating more fat cells may act by redistribution of fat from the intramyocellular compartment into fat cells by providing extra storage depots [27]. Muscle insulin resistance in type 2 diabetes (and obesity) is likely caused by intramyocellular accumulation of lipids (certain fatty acids such as diacylglycerol and fatty acyl CoAs), which block intracellular insulin signaling and cause muscle insulin resistance [9, 10]. The TZDs (rosiglitazone and pioglitazone) may be used alone or in combination with other types of antidiabetic drugs such as metformin or sulfonylureas as well as insulin. The combination of TZDs and metformin for the first time allows for direct targeting of the major pathological defects in type 2 diabetes, reducing hepatic glucose production and increasing muscle insulin sensitivity (stimulating postprandial muscle glucose uptake). The TZDs are generally well tolerated but can, however, cause fluid retention and are therefore contraindicated in patients with class III and IV heart failure [18]. A review of the studies of rosiglitazone led the FDA to conclude that this medication might increase the risk of heart attacks and angina [28], but left the association as inconclusive [29]. Additionally, there is not enough evidence that the risk of heart attack and angina is any greater with rosiglitazone than with other oral medicines used in the treatment of diabetes. Since troglitazone, the first generation of TZDs, was associated with liver injury, that liver enzymes must be measured before starting therapy and periodically thereafter [30].

As type 2 diabetes progresses in older persons adequate glycemic control is associated with an increased risk of adverse effects as a result of age-related changes in drug metabolism. Recently, incretin therapy has become available as novel oral antihyperglycemic treatment, which may prove significant in older persons [31, 32]. Incretins are gut hormones secreted from enteroendocrine cells into the blood within minutes after eating. The two main categories of incretin therapy currently available are: glucagon-like peptide-1 (GLP-1) analogs and inhibitors of GLP-1 degrading enzyme dipeptidyl peptidase-4 (DPP-4). DPP-4 inhibitors are orally active and they increase endogenous blood levels of active incretins, thus leading to prolonged incretin action. The elevated levels of GLP-1 are thought to be the mechanism underlying their blood glucose-lowering effects. There is accumulating evidence that use of incretin therapy, in particular the DPP-4 inhibitors, could offer significant advantages in older persons. Clinical evidence suggests that the DPP-4 inhibitors vildagliptin and sitagliptin are particularly suitable for frail and debilitated elderly patients because of their excellent tolerability profiles [33]. Importantly, these agents lack the gastrointestinal effects associated with metformin and alpha-glucosidase inhibitors taken alone and have a low risk of hypoglycemia. Specifically, sitagliptin has been approved by the US Food and Drug Administration (FDA) for use with diet and exercise to improve glycemic control in adult patients with type 2 diabetes. In randomized, placebo-controlled trials, sitagliptin provided a good treatment option for patients with type 2 diabetes as a monotherapy, or as an adjunct to metformin or a TZD when treatment with either drug alone provided inadequate glucose control [34]. It is also an alternative therapy for those patients who have contraindications or intolerability to other antidiabetic agents [34].

If oral agents are contraindicated or patients fail to respond, insulin is indicated. Physicians should not refrain from initiating insulin therapy in older diabetic patients

simply because of age, however, insulin use requires that patients or caregivers have functional visual, motor, and cognitive skills. Most elderly diabetics do well on insulin injections [35], but physicians should regularly check the ability of their elderly patients to appropriately use the insulin syringe. As with all elderly diabetic patients the risk of hypoglycemia must be weighed against the benefits of tight glucose control and the realistic reduction of risk from microvascular complications. The short-term risk of hyperglycemia including poor wound healing, dehydration, and hyperglycemic hyperosmolar coma must also fit into this balance making this a decision that the clinician needs to consider carefully and on an individualized basis.

Substantial education and continuously monitoring for the degree of diabetic control and the development of chronic complications is key to the management of elderly diabetics. In addition to home glucose monitoring and regular assessments of glycosylated hemoglobin, ongoing care should include annual eye examinations, monitoring of renal function, and regular foot care [18].

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