1.1 Introduction

Numerous studies have been conducted to investigate the pathogenesis of type 2 diabetes [1]. Unfortunately, elderly patients were systematically excluded from these protocols. We have more recently started to study, in a systematic fashion, the pathophysiological alterations that occur in elderly patients with diabetes. These studies, the details of which will be reviewed in the following sections, suggest that there are many ways in which diabetes in the elderly is unique. Some of the factors that contribute to the high prevalence of diabetes in the elderly are shown schematically in Figure 1.1.

1.1.1 Genetic factors

There are several lines of evidence which suggest that there is a strong genetic component to diabetes in the elderly, although the specific genes responsible have yet to be defined [2]. If you have a family history of type 2 diabetes, you are much more likely to develop the disease as you age [3]. Diabetes is much more common in the elderly in certain ethnic groups [4], while the likelihood that an elderly identical twin will develop diabetes if their sibling is affected is over 80%. Even in elderly identical twins discordant for type 2 diabetes, the unaffected siblings clearly have evidence of abnormal glucose metabolism [5].
Diabetes in old age

Thus, it is clear that alterations in glucose-induced insulin release are an important component of the changes in carbohydrate metabolism with aging. However, the most important pathogenic mechanism underlying the glucose intolerance of aging is resistance to insulin-mediated glucose disposal [2, 6, 11]. Debate persists as to whether the insulin resistance of the elderly is intrinsic to the aging process itself, or is the result of lifestyle factors commonly associated with aging. The consensus of opinion is that the aging process itself is the most important cause of insulin resistance, although lifestyle changes are clearly an important contributing factor. The molecular and cellular changes contributing to insulin resistance are detailed below.

1.1.3 Lifestyle and environmental factors

Despite the strong genetic component, it is abundantly clear that various environmental and lifestyle factors can increase or decrease the likelihood that a genetically susceptible individual will develop the disease in old age. Many older people have coexisting illnesses and take multiple drugs (e.g., thiazide diuretics, antipsychotic drugs), which can allow a latent abnormality in glucose metabolism to develop into full-blown diabetes [12, 13]. Obesity, especially with a central distribution of body fat, and a reduction in physical activity as well as functional decline occur progressively with aging, and these factors are associated with abnormal carbohydrate metabolism and diabetes in the elderly [2, 13–21].

The above information suggests that lifestyle modifications may be of value in the prevention of type 2 diabetes in the elderly, even in patients with a strong family history of the disease. Indeed, the Diabetes Prevention Program found that a combined lifestyle intervention consisting of weight loss and increased physical activity was effective in reducing the incidence of diabetes in elderly patients with impaired glucose tolerance [22].

1.2 Diet and diabetes in the elderly

Diabetes is more likely to develop in older patients who have a diet that is high in saturated fats and simple sugars, and low in complex carbohydrates [14, 23–25]. Moderate alcohol consumption may protect against diabetes in elderly women [26]. It has been suggested that deficiencies of trace elements or vitamins may contribute to the development or progression of diabetes in younger subjects, and it is increasingly recognized that the same may be true in the elderly [13, 23]. Elderly patients with diabetes have exaggerated free radical production, and administration of the antioxidant vitamins C and E to these patients improves both insulin action and metabolic control [27, 28]. Some epidemiologic studies have shown an association between low levels of vitamin D and diabetes in the elderly [29–32] but others have not [33]. To date, there have been no trials to test the hypothesis that treatment with vitamin D in elderly patients predisposed to diabetes will prevent its development. There is a correlation between increased intake of vitamin K and a reduced incidence of diabetes in the elderly [34]. Many elderly patients with diabetes are deficient in magnesium and zinc, and supplements of zinc and magnesium can improve glucose metabolism [35–37]. Increased dietary iron may be associated with an increased risk of diabetes in aged individuals [38]. Although chromium deficiency has been shown to cause abnormalities in glucose metabolism in animals and younger patients, there is no evidence to date that chromium supplements will improve glucose tolerance in the elderly. There is also no evidence that selenium deficiency is associated with an increased risk of diabetes in the elderly [39]. Persistent organic pollutants

and byproducts of plastics have been associated with diabetes in some studies [40, 41]. In summary, there is increasing evidence to suggest that dietary abnormalities or environmental factors may contribute to the pathogenesis of diabetes in the elderly, and that modifications of these parameters may be of therapeutic benefit.

### 1.3 Other factors

The presence of inflammation, as evidenced by elevated levels of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), cathepsin, and C-reactive protein (CRP), is associated with an increased risk of diabetes in the elderly [42–46]. Higher GGT levels, a marker of ongoing inflammation, are also associated with progression to diabetes in this age group [47]. Higher levels of adiponectin (an adipocytokine that increases insulin sensitivity) are associated with a reduced incidence of diabetes in the aged [48–52], whereas the opposite effect occurs with higher levels of fetuin-A, a protein that binds to the insulin receptor and inhibits insulin action. Sex steroid hormone levels also appear to be related to the development of diabetes in the elderly [53, 54]. In particular, higher testosterone levels in women and lower levels in men appear to be associated with an increased incidence of diabetes.

### 1.4 Metabolic alterations

The metabolic alterations which occur in middle-aged subjects with type 2 diabetes have been extensively characterized [1]. When compared to age- and weight-matched controls, both lean and obese middle-aged subjects have elevated fasting hepatic glucose production, a marked resistance to insulin-mediated glucose disposal, and a profound impairment in glucose-induced pancreatic insulin release.

Recently, metabolic factors have been characterized in lean and obese elderly patients with diabetes [55–58]. These studies have demonstrated some surprising differences in the metabolic profile between middle-aged and elderly subjects. In contrast to younger subjects, fasting hepatic glucose production is normal in both lean and obese elderly subjects (Figure 1.2). Similar to younger subjects, lean elderly patients have a profound impairment in pancreatic insulin secretion but, in contrast to the young, these patients have minimal resistance to insulin-mediated glucose disposal (Figures 1.3 and 1.4). In contradistinction to the young, obese elderly subjects have relatively preserved glucose-induced insulin secretion (see Figure 1.3), although pulsatile insulin secretion is clearly altered [8]. Similar to the young, however, these patients have a marked resistance to insulin-mediated glucose disposal (Figure 1.4). In summary, the principal defect in lean elderly subjects is impaired glucose-induced insulin release, while the principal defect in obese patients is resistance to insulin-mediated glucose disposal.

The ability of insulin to enhance blood flow is markedly reduced in obese, insulin-resistant older patients with diabetes (Figure 1.5) [57]. Insulin-mediated vasodilation is thought to account for about 30% of normal glucose disposal, presumably because it increases the delivery of insulin and glucose to muscle tissue. Indeed, it has been demonstrated that angiotensin-converting enzyme (ACE) inhibitors may improve insulin sensitivity in elderly patients with diabetes and hypertension [59]. This suggests that drugs which enhance muscle blood flow may prove to be valuable adjuncts in the future for the therapy of elderly patients with diabetes.

Autoimmune phenomena play a pivotal role in the β-cell failure that occurs in patients with type 1 diabetes [60]. It is increasingly recognized that a subset of
middle-aged patients with type 2 diabetes have a form of diabetes that is characterized by β-cell failure, and these patients often have high titres of islet cell antibodies and antibodies to glutamic acid decarboxylase (GAD), similar to younger patients with type 1 diabetes. These patients are said to have latent autoimmune diabetes in adults (LADA) [61–64]. It is tempting to speculate that autoimmune phenomena contribute to the profound impairment in glucose-induced insulin secretion seen in lean older patients with type 2 diabetes. However, the clinical significance of elevated antibodies in the elderly is less certain. Some studies have found that elderly patients with diabetes who are positive for GAD have impaired β-cell function relative to controls without these antibodies, but others have not [65, 66]. It has been suggested that screening for auto-antibodies should be performed in elderly patients with impaired glucose tolerance (IGT) and newly diagnosed diabetes in order to help predict which patients will develop islet cell failure. Although this is a compelling idea, we should only begin widespread screening when randomized studies have demonstrated that early intervention will protect the β

**Figure 1.3** Glucose-induced insulin release in healthy elderly controls and elderly patients with diabetes. Insulin values were measured at glucose levels approximately 5 mmol/l above fasting levels.

**Figure 1.4** Insulin-mediated glucose disposal rates in healthy elderly controls and elderly patients with diabetes. Glucose disposal rates were measured utilizing the euglycemic clamp technique. In this technique, insulin is infused to achieve levels occurring after a meal, and glucose is infused simultaneously to prevent hypoglycemia.

**Figure 1.5** Insulin-mediated blood flow in obese middle-aged controls and obese elderly controls and patients with diabetes. Blood flow was measured in the calf during euglycemic clamp studies utilizing venous occlusion plethysmography.
cells and reduce the need for insulin therapy [63, 64]. Thus, it is unclear at present whether the measurement of autoimmune parameters can be used to predict future insulin requirements in the aged, or whether elderly patients with these abnormalities should be treated with therapies designed to modify autoimmune destruction of the pancreas.

Based on the above information, it is believed that the therapeutic approach to diabetes in the elderly should be different. In middle-aged patients, many endocrinologists recommend that patients be treated with drugs that both stimulate insulin secretion and improve insulin sensitivity, on the assumption that most patients have multiple metabolic problems. However, in lean elderly subjects the principal defect is an impairment in glucose-induced insulin secretion, and the main approach should be to administer secretagogues to stimulate insulin secretion, or to administer exogenous insulin. In obese elderly patients, the principal defect is insulin resistance; hence, patients should be treated initially with drugs that enhance insulin-mediated glucose disposal, such as metformin.

1.4.1 The incretin pathway

The enteroinsular axis refers to hormones released from the gut in response to nutrient ingestion that result in enhanced glucose-induced insulin release, known as the “incretin effect.” The most important incretin hormones are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). When compared to younger controls, both basal and glucose-stimulated GIP and GLP-1 levels have been found to be unchanged or to be increased in healthy elderly subjects, and elderly patient with diabetes [67–70]. The level of dipeptidyl peptidase IV (DPIV), the enzyme that breaks down GIP and GLP-1, is progressively reduced with aging and diabetes. β-cell responses to GIP are reduced in normal elderly subjects and are absent in elderly patients with diabetes [71, 72]. In contrast, β-cell responses to GLP-1 are preserved in the elderly patient with diabetes [73]. These data suggest that GLP-1 and its analogues may prove to be useful therapeutic options in the elderly. This also suggests that agents which prevent the breakdown of GLP-1, such as DPIV inhibitors, may be less effective, although recent clinical trials do not support this hypothesis.

1.4.2 Glucose effectiveness or non-insulin-mediated glucose uptake

It has been recognized for many decades that insulin is an important hormone involved in the uptake of glucose into cells. It has also been demonstrated that glucose can stimulate its own uptake in the absence of insulin [74], an effect that is known as “glucose effectiveness” or non-insulin-mediated glucose uptake (NIMGU). Under fasting conditions, approximately 70% of glucose uptake occurs via glucose effectiveness, primarily in the central nervous system. After a meal, approximately 50% of glucose uptake in normal subjects occurs via NIMGU, with the bulk occurring in skeletal muscle. Because many middle-aged subjects with diabetes are insulin-resistant, it has been suggested that up to 80% of postprandial glucose uptake in these patients may occur via glucose effectiveness. At the present time it is uncertain whether defects in NIMGU contribute to elevated glucose levels in middle-aged patients with diabetes, as studies which have evaluated this parameter have provided inconsistent results.

In healthy elderly subjects glucose effectiveness is impaired during fasting, but is normal during hyperglycemia [75]. Elderly patients with diabetes have an even greater impairment in glucose effectiveness than healthy elderly subjects (Figure 1.6) [76]. Although the cause of

![Figure 1.6](image-url)
this abnormality is uncertain, it may relate to a decreased ability of glucose to recruit glucose transporters to the cell surface.

In the future, this metabolic abnormality may prove to be of great therapeutic relevance to the elderly. In younger patients, exercise, anabolic steroids and a reduction in free fatty acid levels have been shown to enhance glucose effectiveness [74]. Since we have shown that the incretin hormone GLP-1 may enhance NIMGU in elderly patients with diabetes [77], it is possible that future therapies for the elderly may be directed not only at increasing insulin secretion and reversing insulin resistance, but also at enhancing glucose effectiveness.

1.5 Molecular biology studies

At present there is limited information available regarding molecular biological abnormalities in elderly patients with diabetes. The glucokinase gene controls the glucose sensor for the β cell, and defects in this gene could lead to the impairment in glucose-induced insulin secretion in lean elderly patients with diabetes. To date, evidence for mutations in this gene in the elderly is conflicting [78, 79].

In skeletal muscle, insulin binds to its receptor, resulting in activation of the insulin receptor tyrosine kinase. Activation of this enzyme sets in motion a cascade of intracellular events that results in the translocation of glucose transporters to the cell surface. In theory, a defect in any of these pathways could lead to insulin resistance. To date, these intracellular processes have been incompletely studied in elderly patients with diabetes, but the preliminary information suggests that while insulin receptor numbers and affinity are normal, the insulin receptor kinase activity may be defective [80]. Recent data have suggested that mitochondrial dysfunction contributes to insulin resistance in middle-aged patients with diabetes, and potentially also to impairments in glucose-induced insulin release [81]. Age-associated reductions in mitochondrial number and function, possibly due to cumulative damage by reactive oxygen species (ROS), predispose the elderly to ectopic lipid accumulation and insulin resistance in muscle and liver [2, 8, 82, 83]. Preserving mitochondrial function by reducing mitochondrial oxidative damage may be a therapeutic target for preventing an age-associated reduction in mitochondrial function, insulin resistance, and type 2 diabetes. Although normal aging is characterized by progressive mitochondrial dysfunction, to date no studies have been performed to assess mitochondrial function in elderly patients with diabetes [83]. Clearly, further studies are required to elucidate the subcellular defects that cause abnormal glucose metabolism in the elderly patient with diabetes.

1.6 Glucose counter-regulation

Numerous studies have demonstrated that elderly patients with diabetes, when compared to younger patients, have an increased frequency of severe or fatal hypoglycemia [13, 84, 85]. Hypoglycemia is the second most common cause of iatrogenic admission to the hospital in the elderly [86]. Asymptomatic hypoglycemia is very common and can be prolonged [87], and it is frequently associated with cardiac abnormalities [88]. Several studies have evaluated glucose counter-regulation in elderly subjects in an attempt to determine the cause of the increased frequency of hypoglycemia, and a number of important observations have emerged. Many elderly patients with diabetes have not been educated about the warning symptoms of hypoglycemia and as a result do not know how to interpret these symptoms when they occur [89].

The most important hormone in the defense against hypoglycemia in normal subjects is glucagon. If glucagon responses are deficient, epinephrine becomes important, and growth hormone and cortisol come into play if hypoglycemia is prolonged. The responses of both glucagon and growth hormone to hypoglycemia are impaired in healthy elderly subjects, and to an even greater extent in older patients with diabetes (Figure 1.7) [90], although the responses do not differ from middle-aged patients with diabetes [91]. Yet, even when they are educated about the symptoms of hypoglycemia, the elderly have a reduced awareness of the autonomous and neuroglycopenic warning symptoms at glucose levels that would elicit a marked response in younger subjects (bremer, meneilly). Finally, elderly patients have an impaired psychomotor performance during hypoglycemia [90, 91], which would prevent them from taking steps to return the blood glucose value to normal, even if they were aware that it was low. Thus, the increased frequency of hypoglycemia in the elderly is due to a
constellation of abnormalities, including reduced knowledge and awareness of the warning symptoms, decreased counter-regulatory hormone secretion, and altered psychomotor performance.

Levels of pancreatic polypeptide (PP) are elevated during hypoglycemia, and this response is mediated by the vagus nerve. The role of PP in normal glucose counter-regulation is uncertain, but in younger patients with diabetes a reduced PP response to hypoglycemia is an early marker of autonomic insufficiency. Although elderly patients with diabetes often have evidence of autonomic dysfunction, their PP responses to hypoglycemia are normal [92]. Thus, PP responses to hypoglycemia cannot be used to predict autonomic function in elderly patients.

Based on the above information, there are a number of interventions that can be proposed to prevent hypoglycemic events in the elderly. First, it would seem prudent to educate elderly patients about the warning symptoms of hypoglycemia so that they can appreciate them when they occur. Second, consideration should be given to the use of oral agents or insulin preparations that are associated with a lower frequency of hypoglycemic events in the elderly.

### 1.7 Conclusions

In summary, diabetes in older people is caused by a combination of genetic and environmental factors superimposed on the normal age-related changes in carbohydrate metabolism. The metabolic alterations that occur in elderly patients with diabetes appear to be distinct from those that occur in younger patients. As we gain a greater appreciation of the pathophysiological abnormalities that occur in the elderly, we hope to be able to develop a more focused approach to therapy in this age group. It is only in this way that we will be able to better cope with the epidemic of diabetes in the elderly that will befall us in the coming decades.

### Acknowledgments

The studies described in this chapter were supported by grants from the Canadian Institutes of Health Research and the Canadian Diabetes Association. I gratefully acknowledge the support of the Allan McGavin Geriatric Endowment at the University of British Columbia, and the Jack Bell Geriatric Endowment Fund at Vancouver Hospital and Health Science Centre.

I am especially indebted to my longstanding collaborators in this work, particularly Dr Dariush Elahi and Dr Daniel Tessier. I thank Rosemarie Torressani, Gale Tedder, Eugene Mar, Gail Chin, and Christine Lockhart for technical assistance in conducting these studies.

### References


