Diabetes mellitus has long been recognized as a cause of accelerated aging [1,2]. As the understanding of the metabolic syndrome has evolved, it has been recognized that the interaction of a panoply of factors in the presence of insulin resistance results in accelerated aging [3–5]. This article explores the increasing prevalence of diabetes mellitus with aging and how insulin resistance leads to accelerated frailty, disability, hospitalization, institutionalization, and death [6,7].

Diabetes prevalence

During the last 50 years there has been a marked increase in the number of persons in the United States who have diabetes. In 1958 fewer than 2 million in the United States were diabetic, whereas today the number approaches 16 million. There has been a similar increase in diabetes throughout the world, with alarming recent increases in diabetes in developing nations as well as in the developed world [8].

Diabetes mellitus is a disease of older persons: more than half of all diabetics in the United States are over 60 years of age. The prevalence of diabetes mellitus peaks in persons between 65 to 74 years of age [9] (Fig. 1). Twenty percent of men and more than 15% of women 65 to 74 years of age have diabetes. There is a decrease in prevalence rates in persons 75 years and older. It is important to recognize that in 25% to 41% of persons who have diabetes the diagnosis has not been made [10]. Diabetes mellitus is more common in Hispanics (especially those from Mexico),
African Americans, and Native Americans. The prevalence of diabetes mellitus in nursing home residents varies, but, in general, about one third of nursing home residents have diabetes [11–13]. In the 2004 National Nursing Home Survey, 24.6% of nursing home residents had diabetes [14]. The prevalence was 35.6% in nonwhites. Nursing home residents who had diabetes took more medicine, had a longer length of stay, and were more likely to have emergency room visits.

In the United States the increased prevalence of diabetes has been linked clearly to the obesity epidemic [15,16]. Although this association is true in middle-aged persons, it is less true in older diabetics, many of whom are not excessively overweight [15]. In an older African American cohort in St. Louis, persons who had diabetes were only mildly more obese than non-diabetics [16]. In a study in Mexico City, 31.9% of diabetics were obese [17].

Prevalence of the metabolic syndrome

The metabolic syndrome was first described by Nicholaes Tulp in Holland in the seventeenth century. He termed it the “hypertriglyceridemia syndrome.” In the eighteenth century, G.B. Morgagni described a syndrome that consisted of visceral obesity, hypertension, hyperuricemia, atheroma, and sleep apnea. In the late twentieth century, Gerald Reaven and Ferrannini rediscovered the metabolic syndrome, calling it “syndrome X” and “insulin resistance syndrome,” respectively.

The International Diabetes Foundation [18] has defined the metabolic syndrome as

Central obesity: waist circumference
- > 94 cm for persons of European origin
- > 90 cm for men of Asian origin
- > 80 cm for women

Plus any two of the following:
- Triglycerides > 1.7 mmol/L (150mg/dL)

![Fig. 1. Prevalence of metabolic syndrome and diabetes by age cohort.](image-url)
• Reduced high-density lipoprotein < 1.03 mmol/L (40 mg/dL) in men or < 1.29 mmol/L (50 mg/dL) in women
• Raised blood pressure > 130 mm Hg systolic and > 85 mm Hg diastolic
• Raised fasting blood glucose > 5.6 nmol/L (100 mg/dL)

As with diabetes mellitus, the prevalence of metabolic syndrome increases with age, peaking at just under 45% in 60- to 69-year-olds [19]. Again, it is slightly more common in men than in women. A study in nursing homes demonstrated that approximately half of the residents had insulin resistance or diabetes, and these conditions were linked to poorer function [20].

The full expression of the metabolic syndrome occurs in persons who have a genetic propensity and who overeat and underexercise. This genetic predisposition and life style lead to visceral obesity with increased tumor necrosis alpha and leptin levels and decreased adiponectin levels [21]. Insulin resistance then leads to hyperinsulinemia. The clinical presentation is hyperglycemia, hypertension, hyperuricemia, alterations in coagulopathy (plasminogen activating inhibitor-1 and fibrinogen), decreased high-density lipoprotein cholesterol, increased triglycerides, increased small, dense low-density lipoprotein cholesterol, nonalcoholic steatohepatitis, and myosteatosis (fat infiltration in muscle). With this constellation of symptoms, it is not surprising that the metabolic syndrome is associated with increased disability [22,23].

Genes and type 2 diabetes

Five recent genome-wide association scans have given insight into the genetic basis of type 2 diabetes [24]. The effect sizes of each allele so far identified are very modest (odds ratio < 1.2). The following potential genes have been identified:

• Insulin-degrading enzyme (IDE)
• Homeobox, hematopoietically expressed (HHEX): a transcription factor for pancreatic development
• Insulin growth factor 2 mRNA–binding protein (IGF2BP2), which plays a role in cell proliferation
• Cyclin-dependent kinase (CDKN2A/B), which plays a role in islet proliferation
• Cyclin-dependent kinase 5 regulatory subunit–associated protein 1-like 1 (CDKAL1), which reduces insulin secretion
• Scarcerose like 30a8 (SCL3OA8) thiazolidinedione (TZD) variant, which codes for a pancreatic islet-specific zinc transporter–involved insulin biosynthesis and storage
• Fatso (FTO), an obesity locus
• Peroxisome proliferator-activated receptor gamma (PPAR-γ), which is involved in insulin resistance
• Potassium channel NJ11 (KCNJ11), which codes for a pancreatic beta-cell potassium ATP channel subunit
• Transcription factor 7 like 2 (TCF7L2), which is associated with decreased insulin secretion by modulating the Wnt signaling pathway

The most interesting finding from these studies is that only two of these genes (PPAR-γ and FTO) are involved in insulin resistance; the other eight play a role in insulin secretion. This finding confirms, as was pointed out a number of years ago, that type 2 diabetes, particularly in older persons, is more dependent on failure of insulin secretion from the islets of Langerhans than on insulin resistance.

A rare genetic defect associated with diabetes and deafness is the maternally inherited 3243A>G mutation in mitochondrial DNA [25]. This deficit seems to enhance aging of the pancreatic β cells, leading to a reduced ability of these cells to synthesize insulin.

**Diabetes mellitus accelerates aging**

At a basic level, diabetes mellitus accelerates the aging process. Diabetes is associated with a decrease in DNA unwinding rate, increased collagen cross-linking, increased capillary basement membrane thickening, increased oxidative damage, and decreased Na⁺K⁺ATPase activity [26,27].

These basic changes result in increased clinical signs of aging. Cataracts occur 2.5 times more commonly in diabetics than in nondiabetics. Diabetics have accelerated atherosclerosis with increased propensity to have a myocardial infarction, stroke, and peripheral vascular disease [28].

Diabetics have an increased prevalence of cognitive decline [29]. Hyperglycemia has been shown to relate directly to poor memory [30]. Diabetics also are more likely to develop vascular dementia and possibly Alzheimer’s disease [31]. Diabetics should be screened regularly for both mild cognitive impairment and dementia using a formal test such as the Saint Louis University Mental Status examination [32].

Diabetics are at increased risk of falling [33] and developing hip fractures [34]. Persons who have diabetes have an increase in functional decline [35] and frailty [36].

Diabetics complain of pain more often than nondiabetics [37], apparently because glucose or advanced glucose end products inhibit the receptors for endorphins.

Like older persons, diabetics are at increased risk for developing incontinence, nocturia, dehydration, and infections. Diabetes mellitus is associated with an increased likelihood of developing pressure ulcers [38].

Alterations of intestinal permeability in persons who have diabetes mellitus increase the propensity for bacterial translocation [39]. This propensity is associated with increased cytokine activation [40]. Increased cytokines have deleterious effects on muscle, red blood cells, the cardiovascular system, the immune system, and cognition [41].
Depression occurs commonly in diabetics and when poorly treated is associated with poor outcomes [15,42]. Overall, diabetes is associated with a decline in quality of life and a decrease in leisure activities, such as reading, gardening, writing letters, and going out socially [43].

**Diabetes and testosterone**

Testosterone levels decline with aging [44]. Recently, a number of studies have found that testosterone levels are low both in diabetics [45] and in persons who have the metabolic syndrome [46]. An 11-year follow-up study found that low testosterone levels were 1.5 times more prevalent in persons who had metabolic syndrome and were more than twice as prevalent in persons who had diabetes [47].

A number of studies have suggested that testosterone may reduce insulin resistance [48]. In addition testosterone replacement decreases adipose tissue [49]. Smith and colleagues [50] reported that androgen-deprivation therapy for 3 months in men who had prostate cancer resulted in an increase in fat mass and median serum insulin as well as augmentation of central arterial pressure. Recently, androgen-deprivation therapy was shown to be associated with a 1.44-increased risk of diabetes [51]. This increased risk of diabetes produced an increased risk of coronary artery disease, myocardial infarction, and sudden cardiac death. Orchiectomy produced similar effects. Diabetics who have low testosterone or bioavailable testosterone levels may benefit from testosterone replacement [52].

**Hypertension and diabetes**

The study by the United Kingdom Prospective Diabetes Study Group clearly showed that in middle-aged diabetics treatment of hypertension had the best reduction in myocardial infarction and total mortality [53]. Three major hypertension trials (Systolic Hypertension in the Elderly, Systolic Hypertension in Europe Trial and Heart Outcomes Prevention Evaluation Study) demonstrated that lowering blood pressure in diabetics leads to a reduction in stroke, myocardial infarction, and mortality [54]. In addition, some studies have suggested that treatment with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker may decrease the risk of developing diabetes [55]. Control of hypertension often is inadequate in persons who have diabetes [56].

**Diabetes and blood pressure**

Persons who have diabetes often have autonomic neuropathy, which is a major risk factor for orthostasis [57]. Orthostatic hypotension is associated with falls and increased cardiovascular events and death [58].
Persons who have diabetes mellitus are at increased risk of developing postprandial hypotension [59]. Postprandial hypotension results in increased falls, syncope, myocardial infarction, and death [60]. Although the mechanism by which postprandial hypotension develops is unclear, it is associated with rapid gastric emptying [61]. In addition, the release of vasodilation peptides, such as calcitonin gene-related peptide, seems to play an important role in producing peripheral vasodilatation, which produces the syndrome [62]. Recently, it has been shown that an increase in glucagon-like peptide-I slows gastric emptying and reduces postprandial hypotension [63]. Both the alpha-1-glucosidase inhibitors increase glucagon-like peptide I and can be used to attenuate postprandial hypotension [64,65].

**Diabetes and lipids**

It is well recognized that hyperlipidemia interacts synergistically with diabetes to produce cardiovascular disease [66]. A recent meta-analysis has shown that the use of statins has beneficial effects in the treatment of persons between 70 and 80 years of age [67]. There are few data in persons over the age of 80 years, although the Prospective Study of Provastatin in Elderly at Risk study failed to find an effect of pravastatin on mortality, function, or mental status in persons over the age of 80 years [68]. The major negative effects of cholesterol seem to be associated with the occurrence of small, dense low-density lipoprotein, and awareness of that association may help in the decision of whether to use statins in the old-old.

Recent studies have shown that increasing fish and fish oils in the diet has a positive effect on hyperlipidemia [69]. Lipid control in persons who have diabetes living in nursing homes often is inadequate [70,71].

**Diabetes and weight loss**

With aging many older persons develop anorexia [72], which has been characterized as “the anorexia of aging” [73]. Weight loss has been associated consistently with poor outcomes in older persons. A single study in older diabetics found that weight loss was related to an increased hazard of death [74]. Studies in nursing home residents have failed to demonstrate a benefit of diabetic diets [75].

These findings need to be contrasted with three studies in middle-aged and young-old persons that showed that lifestyle interventions consisting of diet and exercise consistently slowed the onset of diabetes mellitus [76,77]. This finding also was true in persons aged over 60 years, and metformin failed to be protective in this group [78]. The author and his colleagues strongly believe that diet modification needs to be associated with exercise (aerobic, resistance, and balance exercises) if it is to have positive outcomes [79].
Reasons for maintenance of euglycemia in older diabetics

There are a variety of reasons to maintain euglycemia in older persons:

- Prevention of hyperglycemic comas
- Prevention of long-term complications
- Prevention of glucose toxicity
  - Accelerated aging
  - Trace mineral deficiency
  - Infection
  - Dehydration
  - Incontinence/nocturia
  - Reduction in pain perception
  - Cognitive dysfunction

Although the most common hyperglycemic coma with type 2 diabetes is hyperosmolar coma, older persons often have a mixed hyperosmolar/ketotic coma [80]. Lactic acid coma also is more common in older persons. These comas often are precipitated by an inciting event, such as a myocardial infarction. In addition, there is increasing evidence that control of excessive glycemia improves outcomes in older persons who are hospitalized, especially for surgical procedures [81].

Age conspires with poorly controlled diabetes mellitus to accelerate the long-term complications of retinopathy, nephropathy, and neuropathy. In older persons, treatment of diabetes decreases the rate of progression of retinopathy [82].

Hyperglycemia accelerates the aging process by producing increased advanced glucose end products, oxidative damage, and DNA breaks [27]. The physiologic age of the average diabetic is 10 years older than the person’s chronologic age.

Hyperglycemia is an ideal environment for bacterial growth. Diabetics are more likely than nondiabetics to have recurrence of tuberculosis [83]. Diabetics often have atypical infections such as mucormycosis and candidiasis [84].

Hyperglycemia causes an increase in urinary fluid loss leading to an increase in incontinence and nocturia [85]. In addition, the hyperosmolar diuresis leads to dehydration. This diuresis also leads to loss of trace elements, causing hypomagnesemia and zinc deficiency [86]. Zinc deficiency can lead to worsening hyperglycemia immune dysfunction and pressure ulcers [87].

Persons who have diabetes mellitus complain of more pain than other persons. Hyperglycemia leads to an increased perception of pain [37] that seems to be caused by glucose interfering with the endorphin receptors.

Numerous studies in humans and animals have demonstrated that diabetes is associated with cognitive dysfunction [88]. Lowering glucose levels improves cognitive function [30]. Dementia is more common in persons who have diabetes mellitus [89].
Overall, all these issues argue for the importance of adequate control of hyperglycemia in older persons who have diabetes mellitus.

References


