1 Epidemiology and Pathophysiology

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Key Points

- Diabetes is common in older adults (age ≥ 65 years).
- The development of type 2 diabetes in older adults is multifactorial.
- Lifestyle and environmental factors are strong diabetes risk factors.
- Older adults with diabetes are at risk of hypoglycaemia due to changes in glucose counter-regulation. Hypoglycaemia should be avoided in this population.

Introduction

Diabetes mellitus is a chronic medical condition and a major global public health issue that affects millions of people worldwide. It can lead to micro- and macrovascular complications, increased morbidity, reduced life expectancy and significant healthcare expenditure [1]. There is an association between increasing age and the development of diabetes, and its prevalence is highest for older adults (age ≥ 65 years) [1]. This population is heterogenous with varying levels of complexity, geriatric syndromes, functional status and life expectancy. In this chapter, the epidemiology and pathophysiology of diabetes in older adults are discussed.

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Epidemiology

In 2019, there were nearly 136 million people worldwide between the ages of 65 and 99 years living with diabetes. This number is anticipated to rise to 195 million by 2030 and 276 million by 2045, based on projections from the International Diabetes Federation (IDF) Diabetes Atlas [2].

The IDF has organised the world map into seven regions for epidemiology research: North America and the Caribbean, South and Central America, Middle East and North Africa, Europe, Western Pacific, South-East Asia and Africa. In 2019, the highest diabetes prevalences in older adults were in the North America and the Caribbean, and Middle East and North Africa regions, at 27.0% and 24.2%, respectively. The Africa and South-East Asia regions had the lowest diabetes prevalence in older adults [2].

Diabetes prevalences among older men and women were similar across the regions, apart from a few exceptions. In North America and the Caribbean, men had higher rates of diabetes (31.0%) compared with women (23.6%). In contrast, in South and Central America, rates of diabetes in women were higher (24.6%) compared with men (20.3%) [2]. In terms of socioeconomic status, high-income countries tended to have a higher diabetes prevalence in older adults compared with middle- and lower-income countries [1, 2]. This trend is likely driven by urbanisation. China, the United States of America and India are countries with the largest populations of older adults with diabetes [2].

Recent studies have shown that diabetes prevalence tends to peak between the ages of 75 and 79 years and that type 2 diabetes is the most common type, accounting for approximately 96% of cases [3]. Several risk factors have been identified as strong contributors to the development of type 2 diabetes, in order of highest risk: obesity, diet, environmental and occupational exposures, and tobacco use [3].

With respect to cost, diabetes care has significant healthcare expenditure. In 2021, it is estimated that US$966 billion were spent globally for the management of diabetes in individuals between the ages of 20 and 79 years [1]. A large proportion of the cost was incurred in the North America and the Caribbean region (US$415 billion) and the greatest amount of spending was for men between ages 60 and 69 years (US$132.5 billion) [1]. Unfortunately, there are limited amounts of health expenditure data on individuals above the age of 80 years.

Pathophysiology of Diabetes in Older Adults

The majority of older adults with diabetes will have type 2 diabetes. In contrast, type 1 diabetes is an autoimmune disease that presents in younger patients due to destruction of beta islet cells and lack of insulin secretion [4]. There is a small subgroup of patients who share overlapping characteristics between type 1 and type 2 diabetes and present later in adulthood (age ≥ 30 years). These individuals have latent autoimmune diabetes in adults (LADA) or type 1.5 diabetes, and have diabetes-associated antibodies. They usually do not require insulin until six months after diagnosis [5].

The development of type 2 diabetes in older adults is a result of age-related alterations in glucose metabolism [4]. There are several other factors, such as genetics, lifestyle and environmental changes, inflammation and comorbidities, that contribute to the development of diabetes (Figure 1.1).

There are several contributing factors to hyperglycaemia in older adults, which leads to an imbalance of insulin secretion and insulin resistance and, ultimately, the development of type 2 diabetes. Age-related decreased beta cell mass and function results in reduced insulin secretion in response to glucose. Genetic predisposition increases an individual's risk of developing diabetes. Lifestyle factors such as diets high in simple sugars and saturated fats lead to increased adiposity, which further increases insulin resistance. A lack of physical activity contributes to a loss of lean muscle mass and decreased insulin sensitivity. Chronic inflammation interferes with insulin signalling pathways thereby increasing insulin resistance. Finally, there are comorbidities and medications that will alter insulin secretion and/or increase insulin resistance.

Age-related Alterations in Glucose Metabolism

With ageing, hyperglycaemia primarily stems from impaired beta cell function and poor adaptation to insulin resistance [6]. Beta cell mass and proliferation decrease with age, and there is reduced beta cell sensitivity to glucose [7, 8]. Studies have demonstrated that insulin secretion in response to glucose is diminished in older individuals compared with

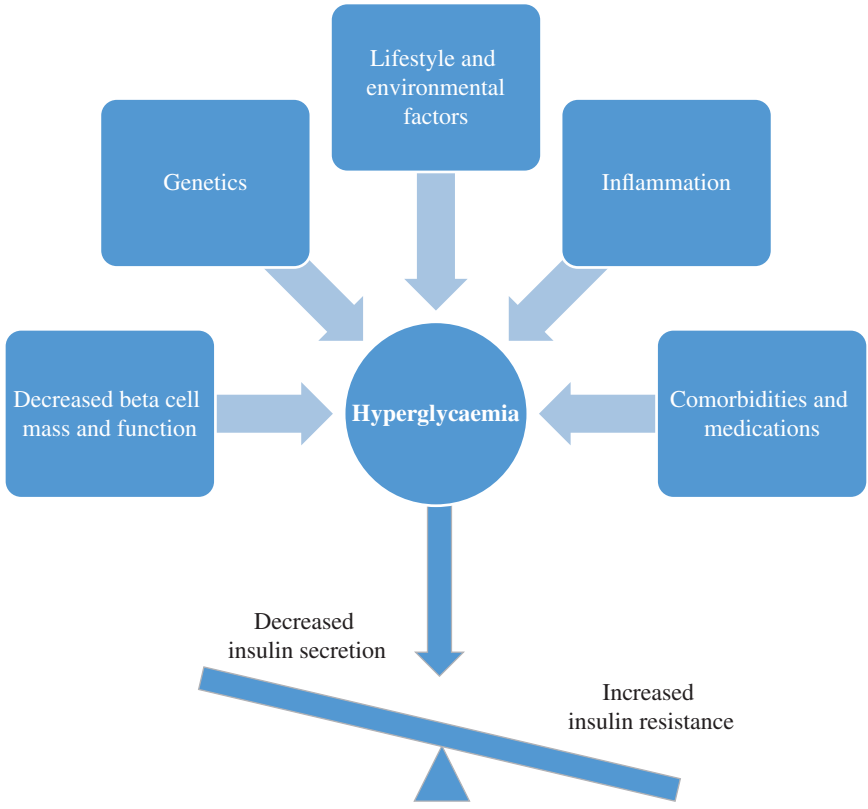

Figure 1.1: Development of type 2 diabetes in older adults.

younger individuals with similar insulin resistance [7]. There was previously a debate as to whether increased insulin resistance and decreased insulin sensitivity were due to the ageing process. However, recent studies have shown that age alone does not increase insulin resistance and that factors such as lifestyle, obesity, lean body mass and sarcopenia are major contributors. Similarly, insulin sensitivity worsens due to increased adiposity and loss of lean muscle mass rather than age alone [6].

There are significant age-related physiological changes that occur in response to hypoglycaemia. In normal and younger individuals, glucagon is secreted by pancreatic alpha cells in response to hypoglycaemia to stimulate liver gluconeogenesis. If the glucagon response is decreased, then the epinephrine response becomes important. When a hypoglycaemia episode becomes prolonged, growth hormone and cortisol are subsequently secreted [9]. In older adults, the response of both

glucagon and growth hormone are impaired during hypoglycaemia. Studies have revealed that the glucagon response is dampened in older adults with diabetes for decreasing blood glucose levels whereas epinephrine and cortisol responses increase [10]. As a result, older adults with diabetes will often have little warning of autonomic and neuroglycopenic symptoms at levels of glucose that would usually elicit symptoms in younger patients. It has also been shown that reaction time is slower in older adults during hypoglycaemia, so they may not be able to act quickly to correct their low blood sugar to the normal level [10].

Genetics

There is a strong genetic component to the development of type 2 diabetes [7]. Older adults with a family history of diabetes are at higher likelihood of developing the condition as they age [8]. However, specific genes leading to the development of diabetes in older age have not been identified. There are also certain ethnic groups that have a higher predisposition to developing diabetes [1].

Lifestyle and Environmental Factors

A diet high in saturated fats and simple sugars, and low in complex carbohydrates and fibre increases the risk of developing diabetes [11, 12]. In addition, diets that incorporate ultra-processed foods (e.g. foods that contain food additives, or undergo multiple physical, biological or chemical processing) have been shown to increase the risk of diabetes [13]. There have been small studies investigating supplementation of vitamins C and E, magnesium and zinc in improving glycaemic control; however, the benefits are not entirely clear [4].

It is not uncommon for older adults to become more sedentary as they age, because of increasing frailty, the presence of geriatric syndromes and multiple comorbidities. These individuals subsequently experience a loss of lean muscle mass and develop sarcopenia, which leads to decreased insulin sensitivity [6]. Physical activity that includes both aerobic and resistance training has been shown to be the most helpful in improving glycaemic levels by increasing insulin sensitivity and decreasing insulin resistance. Given the varying levels of frailty and health complexity, exercise programmes will need to be individualised for each patient [6].

In certain regions, obesity is becoming more prevalent because of poor diet, lack of physical activity and urbanisation [3]. Increased adiposity particularly central adiposity contributes to increased insulin resistance [3, 6]. It has been shown in a large study that individuals who implement healthy lifestyle changes (e.g. body mass index $< 25\,kg/m^2$, diet with low glycaemic load and trans-unsaturated fatty acids, 30 minutes of moderate to vigorous activity per day, no smoking and low alcoholic intake) significantly reduced their risk of developing type 2 diabetes [13].

Other Factors

Inflammation and stress are associated with an increased risk of diabetes in older adults. Proinflammatory cytokines such as C-reactive protein, tumour necrosis factor-α and interleukin-6 inhibit insulin signalling and increase insulin resistance [6]. It has also been suggested that older adults have decreased mitochondrial function and phosphorylation activity, which may contribute to insulin resistance [6]. Furthermore, low levels of sex hormones such as testosterone in men and higher in women have been shown to be associated with increased risk of diabetes [4].

Coexisting comorbidities such as hypertension and obesity increase the risk of developing diabetes in older adults [6]. In addition, acute illness leads to stress-related catecholamine response, thereby inhibiting insulin secretion and increasing insulin resistance. Another contributing factor to hyperglycaemia is medication. Glucocorticoids can cause drug-induced hyperglycaemia by increasing hepatic gluconeogenesis and adipose tissue lipolysis, which in turn leads to increased insulin resistance [6, 14]. Other medications that have been associated with hyperglycaemia include antipsychotics, protease inhibitors, calcineurin inhibitors, thiazide diuretics, fluoroquinolones and some beta blockers [14].

What Are the Key Issues?

Prevention of Diabetes in Older Adults

The number of older adults with diabetes is increasing each year. The complications, morbidity and associated costs have significant implications on the individual, their family and the healthcare system.

Unfortunately, factors such as genetics and age-related changes in glucose metabolism are non-modifiable. However, lifestyle and environmental factors are modifiable diabetes risk factors. Interventions focusing on nutrition and physical activity are important to implement throughout an individual's lifespan. The Diabetes Prevention Program study revealed that lifestyle interventions (diet, physical activity and education) reduced the incidence of diabetes by 58% and was significantly more effective than metformin [15]. Identifying individuals at risk of developing diabetes or with prediabetes will be critical in providing them with management strategies to reduce the risk of progression as they age.

Hypoglycaemia

Older adults with diabetes are at risk of severe and fatal hypoglycaemia due to age-related physiological changes [4]. Hypoglycaemia unawareness is common in older adults. Hypoglycaemic episodes can result in emergency department visits or hospitalisations with falls, cardiac arrhythmias, seizures, delirium, coma and even death. Severe episodes of hypoglycaemia can also increase the risk of developing dementia [16]. Therefore, it is imperative to prevent hypoglycaemia in older adults.

Management

The management of diabetes in older adults requires careful clinical considerations given the age-related physiological changes described earlier (Table 1.1). A collaboration between the primary care physician, endocrinologist, diabetes nurse educator, dietitian and social worker is essential to provide tailored care for older adults with diabetes. Diabetes management strategies for older adults are discussed in later chapters.

Summary

Diabetes is a common chronic medical condition in older adults. The prevalence of diabetes tends to increase with age and is highest in high income countries. The development of diabetes in older adults is due to age-related changes in glucose metabolism along with genetic, lifestyle and environmental factors. Changes in glucose counter-regulation predispose older adults with diabetes to severe and fatal hypoglycaemia,

Table 1.1: Clinical considerations given the physiological changes associated with ageing and diabetes.

Age-related physiological changes	Clinical considerations
Glucose counter-regulation (increased risk of hypoglycaemia)	Education should be provided with respect to signs and symptoms of hypoglycaemia, and how to correct accordingly.
	Management strategies should include efforts to prevent hypoglycaemia episodes. Avoid medications with high risk of hypoglycaemia such as sulfonylureas, meglitinides and insulin if possible. If patients require the use of these medications, then increased monitoring of blood glucose (glucometer or continuous glucose monitor) is needed and close follow-up.
	For patients who are on basal insulin, consider prescribing the insulin in the morning so the effect of the medication wears off overnight when the patient is sleeping and unable to recognise hypoglycaemic symptoms.
Increased adiposity	Nutritional education and counselling should be provided, focusing on decreasing intake of foods with high glycaemic load and saturated fats and avoiding ultra-processed foods. In circumstances of obesity, reduced caloric intake should be considered.
	Prescribe individualised exercise programs focusing on aerobic and resistance training and encourage less time spent in daily sedentary behaviour.
	In select patients, consider using GLP-1 receptor agonists to improve glycaemic control and reduce weight.
Loss of lean muscle mass	Prescribe individualised exercise programmes focusing on resistance training. Balance exercises should also be incorporated to reduce the risk of falls in the setting of sarcopenia.
	Nutritional counselling to be provided to increase protein intake to 1.0–1.5 mg/kg/day if patients do not have contraindications.

GLP-1, glucagon-like peptide-1.

so careful attention is required to avoid hypoglycaemia. Prevention of diabetes and individualised diabetes management strategies are important as this heterogenous population continues to grow and age.

Clinical Practice Question

Q1. Mrs Smith is an 86-year-old woman living alone who was diagnosed with type 2 diabetes approximately 20 years ago. She also has hypertension, dyslipidaemia and chronic kidney disease (estimated glomerular filtration rate 25). Her most recent haemoglobin A1c (HbA1c) was 9.0%. She has been losing weight despite eating three meals per day (primarily simple carbohydrates). Mrs Smith does not exercise but can mobilise short distances using a four-wheeled walker in her apartment. Her diabetes medications include insulin glargine 24 units at bedtime and linagliptin 5 mg daily. She checks her blood sugars fasting and the range is between 7.8 and 11.0 mmol/l (140–198 mg/dl). What is the next step?
Choose one option:

- **A.** Increase insulin glargine to 26 units at bedtime
- **B.** Stop linagliptin and start mealtime insulin.
- **C.** Increase the frequency of glucose monitoring over the next two weeks for glucose pattern analysis and follow-up.
- **D.** Refer for dietitian consultation.
- **E.** Encourage physical activity (walking and resistance bands) 10 minutes after each of her meals.
- **F.** All the above.
- **G.** A, C, D and E.
- **H.** C, D and E.

References

Key references only are listed here. For a full list of references visit: `https://www.wiley.com/go/sinclair/1e`.

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