**CHAPTER 5**

**Diabetes and Ageing – from treatment goals to Pharmacological therapy**

**Abstract**

Diabetes Mellitus denotes a group of common metabolic disorders that share the common phenotype of hyperglycemia. It is becoming one of the most widespread health issues in all age groups . People living with diabetes have a higher risk of morbidity and mortality than the general population. As per IDF (International Diabetes Federation), the prevalence of diabetes in adults aged 20–79 years was estimated to be 8.8% in 2015 and predicted to rise to 10.4% in 2040. (1)As per data by ICMR- INDIAB -17, Prevalence of diabetes is 11.4% , while that of prediabetes if 15.3%(2).Older adults with diabetes are at an increased risk of various complications, such as cognitive decline, dementia, urinary incontinence, osteoporosis, falls, fractures, disability, and medication side effects. These issues significantly impact quality of life and can interfere with effective diabetes management. As a result, managing type 2 diabetes in elderly patients has become a growing concern.

The American Diabetes Association recommends an HbA1c target of less than 7% for older adults who have good cognitive and functional abilities and few chronic conditions, while an HbA1c target of less than 8% is advised for those with multiple comorbidities or cognitive impairment.(3)

Diabetes management and antihyperglycemic treatment should be personalized based on the patient's comorbidities and the duration of their diabetes. It is essential to prioritize medications that have a low risk of causing hypoglycemia. Safe antihyperglycemic options for older patients with type 2 diabetes include metformin (the first-line treatment), pioglitazone, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 receptor agonists. Insulin secretagogues, such as sulfonylureas, should be used cautiously due to the increased risk of hypoglycemia. If sulfonylureas are used, short-acting versions like gliclazide or glinides like repaglinide are preferred. When insulin therapy is necessary, careful attention must be given to the risk of hypoglycemia, and tight glycemic control should not be the primary goal.(3)

**INTRODUCTION**

Life expectancy refers to the average number of years a newborn is expected to live, assuming that current mortality rates remain unchanged throughout their lifetime. Between 2006 and 2016, global mortality rates from non-communicable chronic diseases (NCDs) such as cardiovascular and respiratory diseases, cancer, and diabetes showed a steady decline. However, with the increasing number of individuals aged over 65, the prevalence of NCDs in the elderly has risen, leading to a higher number of years lived with morbidity and disability. Diabetes, in particular, has become a growing cause of premature death and disability.

Given this context, diabetes in the elderly is a significant concern, as this population is highly diverse, including both newly diagnosed individuals and those with long-standing diabetes that began earlier in life. The purpose of this review is to explore the optimal glycemic targets and the most suitable treatment options for older adults with type 2 diabetes, in accordance with current guidelines.

**EPIDEMIOLOGY**

Type 2 diabetes represents the most common metabolic disease in older adults. According to the latest estimates of the International Diabetes Federation (IDF), the global diabetes prevalence in 20–79 year olds in 2021 was estimated to be 10.5% (536.6 million people), rising to 12.2% (783.2 million) in 2045. Diabetes prevalence was similar in men and women and was highest in those aged 75–79 years. Prevalence (in 2021) was estimated to be higher in urban (12.1%) than rural (8.3%) areas, and in high-income (11.1%) compared to low-income countries (5.5%). The greatest relative increase in the prevalence of diabetes between 2021 and 2045 is expected to occur in middle-income countries (21.1%) compared to high- (12.2%) and low-income (11.9%) countries.(6)

According to the International Diabetes Federation (IDF), there were 463 million adults with diabetes worldwide in 2019, an average of 1 in 11 adults. Furthermore, there were 4.2 million individuals who died from diabetes and its complications, accounting for about 11.3% of all global deaths(7) .Furthermore, Individuals with diabetes are at higher risk for cardiovascular disease, and age strongly predicts vascular complications , including peripheral vascular disease, heart disease, and stroke(8)

**PATHOPHYSIOLOGY OF DIABETES IN ELDERLY**

Chronological age is a significant risk factor for various geriatric syndromes, including frailty, immobility, and reduced physical resilience. While genetics contribute to the development of metabolic diseases, environmental and behavioral factors play a major role as well. Environments marked by air pollution, pesticide exposure, environmental toxins, smoking, and alcohol use are strongly linked to the rising prevalence of obesity and its associated comorbidities. Moreover, research shows that behaviors such as dietary choices, physical activity levels, and sleep patterns have a profound impact on the risk of metabolic diseases as individuals age.

As people age, there is an increase in systemic chronic inflammation, which leads to oxidative stress, DNA damage, mitochondrial dysfunction, and tissue damage, all of which contribute to metabolic disruptions. Inflammatory mediators like interleukins (IL-1, IL-6, IL-8, IL-13, IL-18), C-reactive protein (CRP), interferons (INF-alpha and beta), transforming growth factor-beta (TGF-b), and tumor necrosis factor-alpha (TNF-a) play a central role in degeneration and the regulation of glucose metabolism.

Aging also impacts body composition, leading to an increase in visceral fat and a loss of lean muscle mass. Lipids and their byproducts accumulate within and around muscle cells, causing mitochondrial dysfunction, impairing fatty acid β-oxidation, and increasing the production of reactive oxygen species (ROS). This leads to lipotoxicity, insulin resistance, and the heightened release of pro-inflammatory cytokines.

With aging, there is a decline in growth hormone and insulin-like growth factor-1 (IGF-1) levels, which contributes to increased fat accumulation, particularly in the abdominal area, as well as insulin resistance (IR) and glucose intolerance. In women, menopause significantly reduces estrogen levels, which can lead to IR, as estrogen helps tissues remain sensitive to insulin. Similarly, in men, the gradual decline in testosterone levels with age leads to increased body fat, loss of muscle mass, and insulin resistance.

**DIABETES IN ELDERLY**

The symptoms of diabetes in older adults are often nonspecific and can include fatigue, lethargy, dehydration, confusion, unexplained weight loss, and urinary tract infections. Common comorbidities include cognitive impairment, disability, depression, apathy, urinary incontinence, hearing and vision problems, as well as a higher risk of falls and fractures. Additionally, elderly patients with diabetes are more susceptible to hypoglycemic unawareness due to factors such as peripheral neuropathy, autonomic dysfunction, and cardiovascular issues.

Therefore, a comprehensive geriatric assessment to evaluate both microvascular and macrovascular complications should be conducted at the time of diabetes diagnosis. Given the diversity of older individuals with diabetes—due to differences in functional status, comorbid conditions, and life expectancy—treatment plans and glycemic targets must be personalized, taking into account the preferences and needs of each patient.

**Cognitive Dysfunction**

Diabetes is a risk factor for the development of dementia of both vascular as well as neurodegenerative (Alzheimer) etiology. -more with Type 2 diabetes -1.5- to 2.5-fold increase in the risk of dementia (19)Prediabetes, poor control, and longer duration of the disease were associated with greater late-life cognitive decline (20)

Etiology of cognitive dysfunction in the aging population is likely to be the combination of ischemic and degenerative pathology(21) .Vascular dysfunction, high blood pressure, hyperglycemia, hypoglycemic events, insulin resistance, and neuroinflammation play a role.(22).Insulin regulates neurons in the central nervous system and affects amyloid β metabolism, which accelerates Alzheimer-related pathology (23)

Cognitive dysfunction has bidirectional impact on the risk of both hypoglycemia and hyperglycemia in patients with diabetes. Any hypoglycemic episode had a twofold higher risk of developing dementia. Similarly, patients with dementia had a three times higher risk of having subsequent hypoglycemic episodes due to unawareness.(24).

Presence of cognitive dysfunction is associated with poor glycemic control likely due to patients’ inability to perform various components of self-management. Also ,hyperglycemia-mediated advanced glycosylated end product production and oxidative stress damage neurons and vascular endothelium leading to cognitive dysfunction. (25)

Diabetes self-care requires cognitive flexibility and the ability to manage tasks such as glucose monitoring, medication or insulin injections, pattern management, and coordinating diet and exercise. As a result, the American Diabetes Association (ADA) recommends neuropsychological screening for individuals over 65 years old during the initial visit and annually thereafter. This screening aims to detect early signs of mild cognitive impairment and depression, using specific tests such as the Mini-Mental State Examination, Montreal Cognitive Assessment, and Geriatric Depression Scale.(26)

**Osteoporosis And Fractures**

Fracture risk is increased in patients with Type 2 Diabetes mellitus, being higher with longer duration, poor glycemic control ,insulin treated patients and with diabetic complications. (27)High fasting glucose variability has been associated with higher risk for hip fracture while those with impaired glucose tolerance are not at increased risk (28)

Type 2 diabetes in elderly have increased risk of fractures – i)increased risk of secondary hypogonadism, which enhances risk of osteoporosis and muscle weakness in men (29).ii)With aging there is osteo- and sarcopenia. iii)Changes in skeletal muscle protein turnover accelerate these alterations ,iv)complications like retinopathy and neuropathy, v) Diabetic nephropathy with concomitant secondary hyperparathyroidism and renal osteodystrophy(30), vi)Hyperglycemia, oxidative stress, and the formation of advanced glycation end products, has a direct effect on bone metabolism, reducing bone turnover, and disrupting bone formation.(30) , vii)low serum vitamin D concentrations, due to obesity, low physical activity, and less sun .Healthy diet and physical exercise important for the prevention and treatment of both diabetes and osteoporosis.

Metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 receptor agonists should be preferred for the treatment of T2D in these patients, whereas strict targets and insulin should be avoided for the fear of hypoglycemia, falls, and fractures. Thiazolidinediones and canagliflozin should be avoided.

The American Geriatrics Society suggests to interrogate older patients about falls at least every 12 months, examine potentially reversible causes of falls (medications, environmental factors, limiting factors) and perform a complete basic evaluation when an injurious fall occurs (31)

**Urinary tract infections and incontinence**

Frequent Urinary tract infections , polyuria and urinary incontinence – are a risk factor for nocturnal awakenings and falls in elderly diabetics.Therefore, as per American Geriatrics Society, an annual screening for urinary incontinence should be performed .

**GLYCEMIC TARGETS IN ELDERLY DIABETICS**

A general framework for glycemic target, BP and dyslipidemia in elderly patients with diabetes as proposed by ADA is as follows: -(32)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Patient characteristics/health status** | **Rationale** | **Reasonable A1C goal\*** | **Fasting or pre-prandial glucose** | **Bedtime glucose** | **Blood pressure** | **Lipids** |
| Healthy (few coexisting chronic illnesses, intact cognitive and functional status) | Longer remaining life expectancy | <7.0–7.5% (<53–58 mmol/mol)  | 80–130 mg/dL (4.4–7.2 mmol/L)  | 80–180 mg/dL (4.4–10.0 mmol/L)  | <130/80 mmHg  | Statin, unless contraindicated or not tolerated |
| Complex/intermediate (multiple coexisting chronic illnesses¶ or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment) | Variable life expectancy. Individualize goals, considering:• Severity of comorbidities• Cognitive and functional limitations• Frailty• Risk-to-benefit ratio of diabetes medications• Individual preference  | <8.0% (64 mmol/mol) | 90 to 150 mg/dL (5.0 to 8.3 mmol/L) | 100 to 180 mg/dL (5.6 to 10 mmol/L) | <130/80 mmHg  | Statin, unless contraindicated or not tolerated |
| Very complex/poor health (LTC or end-stage chronic illnesses’ or moderate-to-severe cognitive impairment or 2+ ADL dependencies) | Limited remaining life expectancy makes benefits uncertain | Avoid reliance on A1C; glucose control should be based on avoiding hypoglycemia and symptomatic hyperglycemia  | 100 to 180 mg/dL (5.6 to 10 mmol/L) | 110 to 200 mg/dL (6.1 to 11.1 mmol/L) | <140/90 mmHg  | Consider likelihood of benefit with statin  |

**Treatment of Diabetes in the Elderly**

Individualized care is necessary for older individuals with T2DM to maximize patient safety and quality of life .Evaluation of all relevant factors like the patient's risk for atherosclerotic disease and diabetes-related comorbidities, medication history, functional status to assess the patient's ability to manage their type 2 diabetes on their own, presence of depression or cognitive impairment, history of falls or urine incontinence, severe hypoglycemia or attenuated awareness of hypoglycemia, and duration of disease- is of paramount importance .

**Lifestyle modification:**

Older patients with diabetes should have adequate calorie intake along with proteins- to combat the associated sarcopenia .Regular exercise should be encouraged, including both aerobic and resistance training.

**Pharmacologic therapy:**

As older adults at increased risk of hypoglycemia, medication classes with low risk of hypoglycemia and with proven cardiovascular benefits are preferred as per latest Guidelines.(32)

**Oral Anti-hyperglycemic Drugs**

**Metformin** reduces glucose levels by decreasing hepatic gluconeogenesis and improving insulin sensitivity without increasing the risk of hypoglycemia. The recommended starting dose is 500 mg once or twice daily, with a maximum dose of 2,500 mg per day, taken with meals. Dose adjustments are necessary if the glomerular filtration rate (GFR) is between 30 and 45 mL/min/1.73 m², and the medication should be discontinued if the GFR is below 30. Common side effects include gastrointestinal issues and the rare but serious risk of lactic acidosis, especially in patients with heart failure or liver dysfunction.

**Thiazolidinediones** (e.g., Pioglitazone) work as insulin-sensitizing agents by activating peroxisome proliferator-activated receptor-g (PPAR-g), influencing gene expression. Pioglitazone offers advantages such as low cost, good efficacy, and no risk of hypoglycemia when used alone. The typical dosage ranges from 15 mg to 45 mg daily with meals. However, it can cause weight gain and fluid retention, so it should be avoided in patients with congestive heart failure (NYHA classes III and IV). It is also generally not recommended for older adults at risk of falls, non-osteoporotic fractures, or bladder cancer.

**Sulfonylureas** are insulin secretagogues that work by stimulating insulin release from beta cells. They should be used with caution in older adults due to the higher risk of hypoglycemia and weight gain. Short-acting agents with a lower risk of hypoglycemia, such as gliclazide, are preferred in this population.

**Meglitinides** are fast-acting insulin secretagogues that stimulate insulin release during meals. **Repaglinide** is particularly effective for managing postprandial hyperglycemia, has a low risk of hypoglycemia, and is safe for use in patients with renal impairment, making it a suitable option for elderly patients with type 2 diabetes.

**DPP-4 Inhibitors** (e.g., linagliptin, saxagliptin, sitagliptin) enhance insulin secretion in a glucose-dependent manner and prolong the activity of GLP-1. These drugs are well tolerated, have a neutral effect on body weight, and carry a minimal risk of hypoglycemia. They also offer superior cardiovascular safety and improve sarcopenic parameters such as fat-free mass, muscle strength, and gait speed, making them a viable treatment option for older adults with type 2 diabetes.

**SGLT-2 Inhibitors** (e.g., empagliflozin, canagliflozin, dapagliflozin) work by increasing urinary glucose excretion and promoting osmotic diuresis. They also lower blood pressure and body weight. Most older adults tolerate SGLT-2 inhibitors well, though there is an increased risk of mycotic vaginal infections. These medications are particularly beneficial in patients with type 2 diabetes and high cardiovascular risk, as they reduce cardiovascular death, non-fatal myocardial infarction, and stroke. They also have renoprotective effects. However, caution is needed when prescribing to the elderly due to the risks of vaginal infections, dehydration, orthostatic hypotension, lower extremity amputations, and bone fractures.

**Injectable Anti-Hyperglycemic Drugs**

**GLP-1 Receptor Agonists (GLP-1RAs)** enhance insulin secretion and inhibit glucagon release in a glucose-dependent manner, promoting weight loss. These drugs are effective at lowering blood glucose levels with a low risk of hypoglycemia. Common side effects include nausea, vomiting, diarrhea, and increased heart rate. GLP-1RAs may also have protective effects on neuronal health and cognitive function.

**Insulin** remains the most effective treatment for type 2 diabetes and can be used regardless of the patient's GFR. However, insulin therapy requires careful monitoring to prevent hypoglycemia and weight gain. Patients need to have unimpaired cognitive, motor, and visual function to effectively manage insulin therapy. Long-acting insulin analogs are preferred due to their lower risk of hypoglycemia and more stable pharmacokinetics compared to human insulin or neutral protamine Hagedorn (NPH) insulin. For faster and more precise glycemic control, elderly patients may benefit from basal insulins, supplemented with prandial rapid-acting insulins (such as aspart, lispro, or glulisine), or ultra-rapid insulins like faster aspart. Alternatively, premixed insulin regimens, which don’t require mixing, may be suitable for older individuals with regular meal patterns and offer similar efficacy to basal-bolus therapy.

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