CLINICAL STUDY

Diabetes in Golden Age: Clinical Perspective and Management

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ABSTRACT

Diabetes, even in adults may not behave the same across the age spectrum. This is true particularly in the very old who may have functional dependence, frailty, dementia, or who are near the end of their lives. Therefore, in the elderly persons with multiple comorbidities, the principal aim should be the prevention of hypoglycemia, through the choice of antidiabetes medicines and less stringent glycated hemoglobin (HbA1c) target. With improved treatments, persons with diabetes are living longer, causing an increased burden on the health care system. This review focuses on persons with diabetes in their eighties and nineties. The challenges of comorbid conditions, frailty, and pharmacotherapy in this vulnerable group must be addressed.

Keywords: Type 2 diabetes, elderly, frailty, sarcopenia, personalized medicine

Introduction

Older adults aged over 65 years presently constitute nearly half of all adults diagnosed with diabetes mellitus[1]. With advancing age, despite no change in total body weight, lean body mass decreases and percent adiposity increases. Sarcopenia refers to universal and involuntary decline in skeletal muscle mass.

In 2020, population aged 80+ years for India was estimated to be 13,284 million persons. Between 1971 and 2020, population aged 80+ years of India grew from 1,960.75 to 13,284.27 million persons rising at an increasing annual rate that reached a maximum of 9.35% in 1976; it then fell to 1.62% in 20202. Population aged 80 and above in India is substantial according to the World Bank collection of development indicators published in 2022[2].

United Nations Population Fund (UNPFA) in "India Ageing Report 2023" reports that the relatively young India of today will eventually turn into a rapidly aging society in. It states that in 2022, there are 140 million aged 60 years and above, comprising around 10.5% of the total population. This is projected to increase to 15% (around 227 million) by 2036. Between 2022 and 2050, the population of India is projected to grow by 18%, while older population will grow by 134%. During year 2022-50 population of persons aged 80+ years will grow 279%[3].

According to the 2020 World Health Organization (WHO) data, life expectancy in India is: 69.5 years for males and 72.2 years for females and the total life expectancy is 70.8 years which gives India a World life expectancy ranking of 117[4]. The life expectancy at birth (years) has improved by +8.68 years from 62.1 years in 2000 to 70.8 years in 2019[5].

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Epidemiology of T2DM in Older Adults

Between 2017 and 2045, the global population of adults aged above 65 years with diabetes mellitus is projected to increase from 122 million to 253 million, in tandem with the estimated increase in the number of adults aged 65 to 99 years from 652 million to 1.42 billion[6].

Increasing trends for incidence of diabetes are predicated for 2045. Prevalence is lowest among adults aged 20 to 24 years (2.2%). Among adults aged 75 to 79 years, the prevalence of diabetes is estimated to be 24% and predicted to rise to 24.7% by 2045. Aging of world population will therefore result in greater number of persons over 60 years with diabetes[6].

Distinctive Features of Older Adults With Diabetes[7]

Older adults with diabetes have the following distinctive features:

- Decrease in muscle, bone density, and increase in fat.
- Diabetes is frequently associated with complications and/or comorbidities.
- Geriatric syndrome frequently occurs/coexist with cognitive impairment. Both share common mechanisms at the molecular level: (Oxidative stress, impaired repair process, autophagy).
- Diabetes in older adults is commonly associated with polypharmacy, which increases the risk of drug-drug interactions.
- Older adults are at increased risk of severe hypoglycemia due to comorbid it is such as progressive renal failure and age-related decline in glucagon secretion.
- Risk of microvascular complications and cardiovascular diseases associated with diabetes is higher.

Pathogenesis of T2DM in Older Adults

The complex interaction of multiple factors responsible for diabetes results in heterogeneity in the pathophysiology, clinical features, and rate of progression of disease among older population. Glucose tolerance and insulin secretion are impaired due to decline in beta-cell function associated with aging[1]. Figure 1 shows the interplay between aging, obesity, and type 2 diabetes mellitus (T2DM).

T2DM is characterized by hyperglycemia, due to beta-cell less distruction dysfunction and varying degrees of insulin resistance. These are accompanied

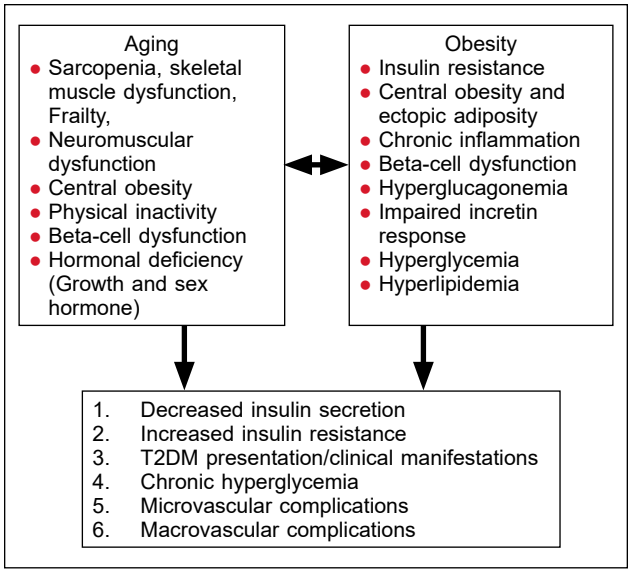

Figure 1. Interplay of aging, obesity, and type 2 diabetes mellitus.

by other counterregulatory disturbances such as hyperglucagonemia and impaired incretin response. Insulin resistance alone is sufficient to stimulate pancreas to increase insulin secretion in the initial stage of T2DM.

Long-term hyperinsulinemia incurs a stress on beta-cells that disrupts the acute (first phase) insulin secretory response to a glycemic stimulus and eventually impairs the later (second phase) insulin response as well. Principally, inadequate insulin secretion is an essential pathogenic component for most patients with T2DM. Aging contributes directly through the decreased

Table 1. ADA Criteria for Prediabetes and Diabetes

Prediabetes	Diabetes
FPG 100 mg/dL to 125 mg/dL = IFG	FPG ≥126 mg/dL
OR	OR
2-Hour PG during 75 g OGTT 140 mg/dL to 199 mg/dL = IGT	2-Hour PG ≥200 mg/dL during OGTT
OR	OR
A1c 5.7%-6.4%	A1c ≥6.5%
	OR
	In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random PG ≥200 mg/dL

ADA = American diabetes Association; FPG = Fasting plasma glucose; IFG = Impaired fasting glucose; PG = Plasma glucose; OGTT = Oral glucose tolerance test; IGT = Impaired glucose tolerance.

beta-cell function that attenuates insulin secretion and indirectly by increasing insulin resistance through obesity and other risk factors[1,8-12].

Ectopic lipid deposits occur in the intracellular compartments, liver, cardiac and skeletal muscles. Intramuscular adipose tissue is a key contributor to insulin resistance in lean older people. Age-related changes in body composition are impaired by physical inactivity, poor dietary habits, associated comorbidities, and the use of medication[13-15].

Screening and Diagnosis of Diabetes Mellitus in the Elderly

The diagnostic criteria for diabetes mellitus in the elderly are similar as in the young. Glycated hemoglobin (HbA1c), although a parameter used to diagnose diabetes mellitus, may be less reliable like in the elderly because of comorbidities, particularly anemia.

Diagnosis of diabetes in the elderly usually follows a routine check-up, or during due to evaluation for a cardiovascular complication, infections (commonly urinary tract), or a lesion of the foot[16].

Endocrine Society guidelines[17], for screening for diabetes or prediabetes in patients aged 65 years and older without known diabetes, include fasting plasma glucose (FPG) and/or HbA1c. In those aged 65 years and older without known diabetes, who meet the criteria for prediabetes by FPG or HbA1c.

Table 1 shows the American Diabetes Association (ADA) criteria for prediabetes and diabetes[18].

Clinical Considerations[1,19-21]

T2DM among older adults is heterogeneous in persention. Differences exist between late-onset T2DM and long-standing T2DM, in clinical presentation, and severity of the disease. The elderly T2DM individuals have compromised functional status, ability to care for themselves and comorbidities[1].

To facilitate common goal setting and frame treatment recommendations, this heterogeneity can be captured in three groups[1].

- The first group comprises individuals in good health with little or no cognitive or functional impairment, and a long-life expectancy (>10-15 years).
- The second group contains those includes with some comorbidities and mild disability.
- The third group includes those who have a high number of comorbidities and/or disabilities and a shorter life expectancy (>5 years).

The above factors after the disease process as compared with younger adults and thereby affect the management of T2DM with and without comorbidities. Several common clinical aspects are considered here, namely the specific care needs relating to frailty and sarcopenia, multimorbidity, and the susceptibility to hypoglycemia.

Assessment of Older Patients with Diabetes[17]

The overall treatment strategy and goals for elderly/older adults with T2DM depends on patients' overall health, comorbidities, and functional status. Functional status refers to a person's ability to perform normal daily activities required to meet basic needs, fulfil usual roles, and maintain health and well-being.

Both aging and diabetes have significant interactions which can adversely impact overall functional status. Considering its complexity, recent diabetes guidelines evolved around care of the aging patient with diabetes, which requires individualized, rather than a purely algorithmic approach.

There is no standard tool in use for the assessment and documentation of functional status of older adults/elderly.

Functional status is most often documented using subsets of specific activities that are necessary for living independently.

- They include activities of daily living (ADLs), that is, bathing, dressing, eating, toileting, and transferring.
- Instrumental ADL (IADLs) that is preparing meals, shopping, managing money, using the telephone, and managing medications.

In patients with diabetes, deficits in IADLs identified during routine evaluation should trigger a more in-depth evaluation of the patient, including detailed assessment of hypoglycemia and hyperglycemia, microvascular and macrovascular complications, and cognition.

Frailty and Sarcopenia in Elderly Patients[22]

With increasing life span, presence of T2DM in the elderly is becoming more prevalent. These patients present with multiple comorbidities like hypertension, cardiovascular disease, dyslipidemia, osteoarthritis, chronic obstructive pulmonary disease, bronchial asthma, etc. Some T2DM patients also have diabetic complications like neuropathy, nephropathy, retinopathy, etc.

Table 2. Fried's Frailty Criteria

Findings
Involuntary weight loss of 10 lbs or more in the last 6 months
Reduced grip strength
Difficulty in initiating movements
Reduced walking speed
Fatigue

Frailty scale: Fit (no abnormalities), Pre-frail (2 abnormalities or less), Frail (3 or more abnormalities)

Other entities especially frailty is independent of the evolution of diabetes in elderly. Frailty, is a standardized phenotype in older adults with a predictive validity for adverse outcomes in geriatric patients. It is an emerging global health burden with important implications for clinical practice and public health.

Fried's frailty criteria are widely used to diagnose frailty (Table 2). The diagnosis is established if the patient meets three of the following criteria: unintentional weight loss, exhaustion, muscle weakness, motor slowness, and low activity. Therefore, nutritional education and physical activity to control glycemic levels are effective in maintaining functional autonomy.

The most common mechanism of frailty in older adults with T2DM are genetic, epigenetic, and environmental factors, along with insulin resistance, arteriosclerosis, chronic inflammation, oxidative stress, and mitochondrial dysfunction. Frailty is associated with mortality and hospitalization in patients with diabetes. Along with hypoglycemia, it is directly linked with accidental falls and hospitalization with worse outcomes. Therefore, it is important to prevent this complication in frail and diabetic patients.

Sarcopenia has a strong impact on quality of life in elderly patients with T2DM. Sarcopenia has low muscle strength as the main characteristic. Common contributors are poor nutrition, body inactivity and chronic diseases, etc.

Sarcopenia has a higher prevalence in T2DM (5%-50%). Sarcopenia associated with frailty and diabetic complications are emerging as an important category leading to disability, dependency, and increased mortality. All this has a high impact on the quality of life which is the main objective in older patients; therefore, early detection of frailty and sarcopenia are key aspects in the management of older patients in general and diabetes in particular.

Chronic systemic proinflammatory states are induced by T2DM, sarcopenia, and frailty which lead to various changes in the immune system. Proinflammatory state leads to tissue damage, sarcopenia, and frailty. These situations interreact with each other and hamper the overall management. Older T2DM patients are commonly observed to have obesity and sarcopenia, defined by concomitant presence of sarcopenia and obesity, which is known as sarcopenic obesity.

Guidelines and Treatment Goals[1]

Guidelines for the treatment of hyperglycemia in older adults with T2DM consider the frequently associated cardiorenal challenges and need to minimize the risk of hypoglycemia. Treatment options need to provide flexibility to adjust treatment goals for frail individuals with comorbidities. Since T2DM in older adults has diverse phenotypes, it is essential to adopt a highly individualized approach that incorporates functional goals as well reduces risk factors.

Good glycemic control can delay the onset and reduce severity of microvascular complications across age groups. However, intensive treatment strategies might be less beneficial in older adults who have frailty and T2DM risk and, increase the possibility of hypoglycemia at old age. Furthermore, the benefits of intensive glycemic control tend to accrue over a long period time and might be less relevant in those with limited life expectancy. Intensive strategies can also be challenging to implement in the presence of comorbidities that restrict therapeutic options.

The criteria need to be individualized and with less stringent treatment intensification in older T2DM, there will be lesser chances of hypoglycemia and other adverse events. Clinical guidelines recommend less stringent control, <8% in older adults who are less fit with long duration of diabetes. HbA1c levels up to 8.5% have been suggested as acceptable in older patients with complex needs and frailty and/or multimorbidity. At the same time, signs and symptoms of microvascular and macrovascular complications need to be addressed appropriately. Glycemic control and targets need to be individualized.

Less stringent glucose target levels, are focused on symptomatic control and minimization of risk of hypoglycemia. Many of these older individuals have complex needs and might not be able to self-manage. Therefore family members, caregivers, and diabetes educators need to be involved to ensure care plans are clearly communicated and implemented.

At the same time, there is a need to pay attention to other cardiovascular risk factors which include blood

pressure, low-density lipoprotein (LDL) cholesterol, which remain integral to the management of T2DM at all ages.

The notion of setting less rigorous targets for older adults than for younger individuals is contentious. Most guidelines suggest blood pressure target goals of ≤140/85 mmHg in older adults but lower targets <130/80 mmHg in patients with microvascular or cardiovascular disease. LDL cholesterol targets are usually <100 mg/dL in all adults but ideally lower target <70 mg/dL are set in patients with cardiovascular disease or a very high cardiovascular risk at all ages.

Nonpharmacological Management[22]

Health Education

Health education for patients and care provider remains a cornerstone of diabetes management. Health education needs to focus on healthy diet, physical activity, medication and improved glucose testing can pay dividends and will benefit from periodic reinforcement.

Therapeutic education is one of the fundamental aspects in the treatment of people with diabetes mellitus. In the case of the elderly with this disease, this activity has peculiarities. At first, a comprehensive evaluation of the patient is recommended to identify physical, mental, or social problems that may interfere with the educational therapeutic process.

The main goal of therapeutic education is to promote self-care and ensure therapeutic adherence without deteriorating the quality of life, while teaching the patient to live with the chronic condition.

Lifestyle

For all age groups with T2DM a balanced healthy diet is recommended. Specifically, a low intake of saturated fats, simple sugars, salt, and the need to adjust portion size and total caloric intake in accordance with desired weight control. However, over-zealous dieting by older adults can accelerate the loss of muscle mass to their detriment. Furthermore, rapid weight loss (intentional or unintentional) might also disguise beta-cell failure and lead to worsening T2DM.

The benefit of even very modest physical activity is well recognized. In older adults with the limiting factors of reduced mobility and comorbidities, bespoke exercises such as "chair-based exercise" that include resistance and/or aerobic components can improve muscle mass and strength, assist glycemic control, and mental well-being[1].

In elderly patients, both aerobic and resistance training prevent and treat the decline in muscle mass and strength. These exercises must be tailored as per individual health status. It is known that resistance training positively influences the neurotransmitter system and increase hormone concentrations and rate of protein synthesis. These changes lead to improved functional independence, self-esteem, and quality of life,

Variable-intensity Exercise Programs

Multiple types of physical exercise have been studied and recommended. If the patient's baseline physical condition is good, exercise such as walking at low-intensity is recommended. Patients unable to walk may ride a stationary bicycle as exercise and look to try other simple exercise such as wide-leg squats, standing leg curls, hip extension, or hip flexion. In patients with severe physical impairment, simpler exercises such as knee extension, ankle circles, arm raise, chair push, tennis ball squeeze, seated neck turn, or leg circles can be attempted[22].

Nutrition[21]

Nutrition is a fundamental pillar of and extremely critical in the management of elderly diabetes patients. Nutritional intake should be individualized based on nutritional status, physical activity level, disease status, and tolerance.

Daily protein intake of 1.0 to 1.2 g/kg body weight is recommended to maintain and restore body mass and function in elderly patients. Adequate diet to maintain good glycemic control is important in persons with T2DM. Malnutrition should be avoided in older patients, especially in patients with frailty or sarcopenia.

Vitamin D is essential to improve muscle mass and strength. Generally frail and sarcopenic patients usually have vitamin D deficiency. Significant improvement is observed in overall muscle mass and function of lower extremities after administration of vitamin D supplements. Vitamin D effects are augmented by supplementation of protein diet and muscular activity in elderly patients with diabetes and sarcopenia.

Vitamin B12 deficiency is highly prevalent in older people, but mostly it is asymptomatic, there is no formal recommendation for screening. With advanced aging, generally intrinsic factor deficiency occurs, therefore absorption of vitamin B12 from intestine is impossible. The relationship between the intake of these supplements and frailty has been studied in some observational studies. However, findings are

inconclusive, hence no formal recommendation is being made here.

The Mediterranean diet is widely considered as the healthiest diet. It is known to reduce the risk of cardiovascular events. Meta-analysis recommended adherence to Mediterranean diet to reduce risk of frailty and functional disability.

Other Recommendations[22]

Physical exercise and a healthy diet are two key aspects in the management of T2DM in the elderly population. Collective and collaborative efforts are required from family members or caregivers to take care of older patients and prevent complications. Modification in day-to-day life to prevent falls and fractures must be implemented in elderly diabetis with frailty and sarcopenia.

Risk of depression is very high in frail patients due to fewer social communication and poor network. Therefore, promoting a healthy social network is a priority to promote the best possible state of mental health.

Cognitive dysfunction is linked with physical frailty, diabetes, and sarcopenia. Therefore, cognitive stimulation programs and other measures that prevent and retard the development of dementia should be promoted encouraged. Social ties, perceived support, and participation in social activities have key role to promote mental health in older age, especially among frail adults.

Finally, the prevention of hypoglycemia must always be the primary focus in frail diabetic patients. It is crucial to know how to identify early signs of hypoglycemia and its management.

Primarily, nutritional education and encouragement for physical activities must be implemented by multimodal and multidisciplinary intervention. The fundamental aim is maintain the best possible functional autonomy in T2DM with risk of frailty or sarcopenia. It is crucial to mention that the benefit of reducing the risk of microvascular complications is lower than the likelihood of serious side effects due to hypoglycemia.

However, patients with poorly controlled T2DM may suffer from acute complications of diabetes, such as dehydration, poor wound healing, or hyperglycemic hyperosmolar coma. Therefore, glycemic goals should primarily avoid these consequences.

Main nonpharmacological measures are summarized in Table 3.

Table 3. Main Nonpharmacological Measures in T2DM with Frailty and/or Sarcopenia

Lifestyle
Physical activities
Nutritional counseling
Improve mental health
Cognitive stimulation
Avoid hypoglycemia
Foster social ties
Fall prevention

Pharmacological Management[1,22]

Biguanides

Lifestyle intervention is always the first step to initiate treatment, followed by metformin as a first-line pharmacotherapy for patients of all age groups. Metformin counteracts insulin resistance and offers glucose-lowering effect with low risk of hypoglycemia. The underlying mechanism of action of metformin in glycemic control includes the reduction of hepatic gluconeogenesis, reduction in appetite, inhibition of glucose absorption, and increase in insulin-mediated glucose utilization in peripheral tissues such as muscle and liver. Data from studies in older adults with T2DM treated with metformin has confirmed that this drug is efficacious and has a favorable safety profile.

Regarding sarcopenia, although the precise mechanisms are not clearly recognized, various studies show that metformin apparently has positive effects on both muscle mass and muscle strength. Newly diagnosed T2DM patients treated with metformin 1,000 mg twice daily had a significant increase in skeletal mass index. Other studies showed that metformin exposure was associated with a lower risk of frailty after adjustment for covariates.

Normal renal function is required for metformin clearance. Dosage adjustment might be needed if estimated glomerular filtration rate (eGFR) declines below 60 mL/min/1.73 m^2. Metformin needs to be stopped if the eGFR falls below 30 mL/min/1.73 m^2. Therefore, monitoring of renal function is essential.

Sulfonylureas

Sulfonylureas have been commonly used due to their affordability. They are ATP-sensitive potassium channel blockers. The release of insulin from beta cells of pancreas is stimulated by these antidiabetic agents. Sulfonylureas are currently less frequently used

especially in the elderly, due to risk of hypoglycemia, weight gain, etc.

Sulfonylureas are effective in the short-term management, often have poor durability of effectiveness. The insulin releasing action of sulfonylureas can continue irrespective of glucose concentration, which poses higher risk of hypoglycemia. Due to risk of hypoglycemia, these drugs are an undesirable choice for older adults with frailty. The risk of hypoglycemia varies between different sulfonylurea preparations. Short-acting sulfonylureas are associated with lower risk of hypoglycemia than long-acting preparations. Among second-generation sulfonylureas, gliclazide is associated with low risk of hypoglycemia; therefore, short-acting sulfonylureas are preferred in older adults.

Meglitinides

Glinides have a similar mechanism of action to sulfonylureas but differ slightly in having a shorter circulating half-life and rapid absorption; they principally lower postprandial glucose levels. Like sulfonylureas, they carry a high risk of hypoglycemia and are not recommended in the elderly. Furthermore, these drugs must be had with meals, so their use is not recommended in frail patients with poor eating habits.

Dipeptidyl Peptidase 4 Inhibitors

Dipeptidyl peptidase 4 (DPP-4) inhibitors inhibit degradation of endogenous glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic peptide (GIP) and thereby increase their actions. GLP-1 is the main incretin, potentiating nutrient induced insulin secretion without causing hypoglycemia or weight gain, and suppressing excess glucagon secretion from alpha-cells.

Majority of DPP-4 inhibitors are eliminated in urine, and except linagliptin, require a reduced dose in renal impairment. Limited trial evidence is available regarding the use of DPP-4 in older adults; however, the safety profile of these agents has been reassuring. The rate of major adverse cardiovascular events (MACE) was not affected using DPP-4 inhibitors in large prospective cardiovascular outcome trial (CVOT) studies, although there have been concerns about a small increased risk of hospitalization for heart failure. Therefore, it is recommended to use DPP-4 inhibitors with caution in older patients with heart failure. These are a good choice of agents in older adults due to low risk of hypoglycemia, good tolerability profile and once a day administration. They do not modify body weight or present significant drug interactions or cause digestive intolerance. These are all important advantages in elderly patients. DPP-4 inhibitors may increase muscle mass, although their mechanism is unclear. It could be related to ability to enhance GLP-1 action or inhibition of DPP-4 activity per se, or both.

Sodium-glucose Cotransporter 2 Inhibitors

Sodium-glucose transporter 2 (SGLT2) inhibitors act by reducing glucose reabsorption from renal filtrate, which decreases blood glucose through glucosuric effects. The glucosuric effect diminishes with lower serum glucose levels, hence preventing hypoglycemia. Glycosuria provides caloric loss which facilitates weight loss. Glycosuria and osmotic diuresis lead to reduction of blood volume and reduced blood pressure. Large CVOT trials with T2DM have demonstrated superior efficacy and safety of SGLT2 inhibitors. Hence, this class of drug is indicated for cardioprotective and renoprotective effects. These drugs showed reduction in heart failure hospitalization and albuminuria, and a slower age-related decline in GFR.

In EMPA-REG and CANVAS trials, more than 40% recruited participants were aged more than 65 years. Subgroup analysis demonstrated that cardiovascular benefit were similar in older and younger adults. Side effects like genital infections or rare events like fractures or lower limb amputation were similar across age groups.

It is essential to have adequate renal function to demonstrate glucosuric action of SGLT2 inhibitors. A GFR ≥ 60 mL/min/1.73 m^2 is generally recommended for best glucose-lowering effect. However, dapagliflozin, empagliflozin, and ertugliflozin can be continued while GFR is >45 mL/min.

The potential renoprotective effects of SGLT2 inhibitors now permit canagliflozin to be started at a low dose if GFR is >30 mL/min/1.73 m^2 and continued even until end-stage renal disease. Decline in GFR presents caution for use of SGLT2 inhibitors in older people with frailty. Volume depletion can occur in older people due to concurrent use of SGLT2 inhibitors and loop diuretics. Considering the risk of volume depletion, compromised peripheral circulation, potential risk of fractures, and lower limb amputation, SGLT2 inhibitors are not suitable for use in very old and frail patients.

GLP-1 Receptor Agonists

Incretin hormones potentiate glucose-mediated insulin response chiefly caused by two peptides, which includes GIP and GLP-1.

Glucose-lowering effect of GLP-1 receptor agonists (GLP-1RAs) involves the potentiation of nutrient

stimulated insulin release and suppression of glucagon release. GLP-1RA actions are glucose-dependent; hence, these drugs produce less hypoglycemia.

GLP-1RAs delay gastric emptying and exert a satiety effect, which helps in overall caloric intake and portion control. These effects facilitate weight loss in patients who are treated with GLP-1RA. A few studies which evaluated GLP-1RAs in older adults with T2DM have shown good efficacy and tolerance. Post hoc analyses of large CVOT trials with GLP-1RAs also indicate that the cardiovascular benefits extend to all age groups, including those aged over 75 years.

GLP-1RA formulations are available in injectable (daily or once a week) and oral formulations. Common side effects are nausea and gastrointestinal symptoms. These agents are mostly degraded in the circulation and can be used with dose adjustment in patients with renal impairment. Although initial concerns were raised regarding the excess risk of acute pancreatitis, the long-term safety profile of GLP-1RAs has been reassuring as evidenced from large CVOTs.

Thiazolidinediones

Thiazolidinediones are ligands for an orphan nuclear receptor peroxisome-proliferator activated receptor-gamma (PPARγ). They exert insulin sparing action by activation of PPARγ. They increase insulin sensitivity by increasing peripheral uptake of glucose in muscle and adipose tissue. They also lower hepatic glucose production to a lesser extent and stimulate oxidation and lipogenesis in adipose tissue.

Thiazolidinediones have much wider therapeutic applications as second-/third-line oral antidiabetic drugs, once a day. They decrease blood pressure, are safer in moderate to severe renal failure, and decrease microalbuminuria. Thiazolidinediones have slow onset of action. The durability of their glucose-lowering efficacy is generally longer and they do not increase the risk of hypoglycemia.

Weight gain, ankle edema, fluid overload and hepatotoxicity are common adverse effect of thiazolidinediones, which could precipitate or exacerbate heart failure. Pioglitazone has similar efficacy across all age groups. In addition, pioglitazone has been reported to protect against the development of some vascular events, including stroke. In addition, pioglitazone is associated with an increased risk of bone fractures, which is common in patients with frailty and detracts from their use in patients with osteoporosis or osteopenia.

Alpha-Glucosidase Inhibitors

These agents are primarily used to reduce postprandial hyperglycemia without increasing the insulin levels. Alpha-glucosidase inhibitors, such as acarbose, delay the absorption of simple sugars from meals rich in complex carbohydrate. Alpha-glucosidase inhibitors do not cause hypoglycemia or weight gain and can usefully reduce interprandial hypoglycemia in insulin-treated patients by prolonging the prandial absorption time. In older adults with T2DM, studies investigating the use of acarbose are limited; however, efficacy seems to be similar to that seen in younger individuals. The abdominal adverse effects of bloating, flatulence, and diarrhea can reduce adherence and any gastrointestinal disease in older adults is a major caution against its use.

Insulin

Patients older than 75 years and/or frail should start insulin therapy or intensify it to multiple daily injections only when other options for glucose control have been exhausted. Insulin therapy is associated with the risk of hypoglycemia. Caution should be taken while initiating insulin especially for those who are living alone, dependent on carers or with serious comorbidities. Basal and Premix or co-formulation insulins can effectively control symptomatic hyperglycemia that is uncontrolled by other agents.

Combination treatments can be considered for selective older patients. Basal insulin and Premix insulin can be considered in combination with oral therapies. The weight gain observed with insulin therapy might be beneficial in older adults with sarcopenia and/or frailty. Insulin is often the only realistic option in those with advanced renal or liver disease. Caution for starting dose and titration schedule needs to be implemented for older adults, and physicians must be aware of comorbidities, cognition function of patient as well as availability of care takers.

Summary

The increasing prevalence of T2DM in older adults is due to improved access to health care and consequent increase in life expectancy. Older onset T2DM tends to progress more slowly than early-onset T2DM. Therefore, treatment targets need to be less stringent compared with those in younger patients. This will help patients make minimum lifestyle changes, experience less hypoglycemia and lead to a better quality of life.

The management plan of older adults with diabetes must take into consideration the heterogeneity of

multiple to morbidities, the functional and cognitive status, and the living conditions of these patients.

Diabetes in people aged above 80 years brings with it associated comorbidities, frailty, sarcopenia, and disability. Therefore, overall management should be individualized considering the needs, possibilities, and risks. HbA1c goals need to be personalized according to life span, comorbidities, and frailty. While choosing treatment options, physician needs to consider the right agents which are relatively free from hypoglycemia and have lower chances of drug-drug interactions.

T2DM, sarcopenia, and frailty are interlinked and often coexist leading to functional disability. Therefore, relaxed glycemic control parameters are recommended, which will ensure prevention of both hypoglycemia and hyperglycemia.

All drugs are approved by regulatory authorities based on randomized controlled trial (RCT) with younger population less than 75 years based on criteria of study. Hence population above 75 years with comorbidities are mostly underrepresented in RCT. Therefore, the practicing physician needs to choose the right drug on available RCT data, clinical acumen, overall drug interactions, kidney function, and overall safety profile. For newer agents, real-life experience is essential to make the right choice based on assessment of elderly patients above 75 years. It is highly encouraged to publish retrospective data on clinical use of various medication in this special population.

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