

Management of Glucose-Lowering Therapy in Older Adults with Type 2 Diabetes: Challenges and Opportunities

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Abstract: The population of older adults (≥ 65 years) with type 2 diabetes mellitus (T2DM) is diverse, encompassing individuals with varying functional capabilities, living arrangements, concomitant medical conditions, and life expectancies. Hence, their categorization into different patient profiles (ie, good health, intermediate health, poor health) may aid in clinical decision-making when establishing glycemic goals and pharmacological treatment strategies. Further granularity in assessing each patient profile through interdisciplinary collaboration may also add precision to therapeutic and monitoring decisions. In this review, we discuss with a multidisciplinary approach how to deliver the best benefit from advanced diabetes therapies and technologies to older adults with T2DM according to each patient profile. There remain however several areas that deserve further research in older adults with T2DM, including the efficacy and safety of continuous glucose monitoring and automated insulin delivery systems, the switch to once-weekly insulin, the effectiveness of multidisciplinary care models, and the use of supported telemedicine and remote blood glucose monitoring in the oldest-old (≥ 85 years) who particularly require the assistance of others.

Keywords: type 2 diabetes, older adults, patient profiles, management

Introduction

Aging, a natural phenomenon, is typically assessed based on an individual's chronological age. Individuals who are 65 years of age or older are considered "elderly".¹⁻⁴ However, with the increase of people's life expectancy worldwide and the improving health and functional status in older people, there has been a redefinition of old age. Some authors define the age from 65 to 74 years as pre-old age, and 75 years or over as old age.¹⁻³ Some studies further classify adults between the ages of 75 and 84 or 89 years as old or middle-old, and those aged at least 85 or 90 years as oldest-old.^{3,4}

As aging progresses, and irrespective of the adopted definition of old age, pathophysiologic changes occur in various organs, including the liver, kidneys, heart, and musculoskeletal system (ie, bone and muscle loss), and the risk of chronic illnesses increases.⁴ Among these chronic illnesses, type 2 diabetes mellitus (T2DM) is a widely prevalent health condition among the older population.⁵ It is estimated that almost one-quarter of people with T2DM are aged 70 years or over.⁶ By altering glucose metabolism, T2DM leads to accelerated biological age, which specifically measures the physiological breakdown of cells and organs. Hence, considering biological age, in addition to chronological age, may also provide a tool to accurately assess healthspan in T2DM.⁷

Older adults with T2DM constitute a diverse group of patients characterized by varying functional capabilities, living arrangements, concomitant medical conditions, and life expectancies.⁸ Moreover, there is broad variation in functional status and health-related quality of life within every age subgroup (ie, from pre-old to oldest-old), with individuals having good and poor health at both ends of the age spectrum.^{8,9} Hence, older adults with T2DM can be fit individuals living

independently in the community, or functionally dependent residents of nursing homes with multiple comorbidities, with in-between a whole spectrum of intermediate health states at risk of deterioration (frail). Older adults can also have either newly diagnosed T2DM or long-standing T2DM with onset in middle or early age.¹⁰ In addition, older adults with diabetes can fall into any of the five clusters that were proposed by Ahlqvist et al: severe autoimmune diabetes, severe insulin-deficient diabetes, severe insulin-resistant diabetes, mild obesity-related diabetes, and mild age-related diabetes.¹¹ Consequently, the pharmacological management of T2DM in older adults can be challenging for clinicians, warranting frequent evaluation of medical, psychological, functional, and social domains.

T2DM management in older adults should aim to achieve a good quality of life and avoid diabetes-related complications as well as treatment side effects, mainly hypoglycemia.^{5,12} Importantly, T2DM management should aim to promote healthy aging, defined as the preservation of functional ability that enables individuals to fulfill their needs and actively participate in society.¹³ Unfortunately, older adults are vastly underrepresented in clinical trials, particularly frail or dependent individuals, resulting in a lack of sufficient evidence-based data to inform clinical decision-making in the population of older patients with T2DM.⁸ In light of recent guidelines on the management of T2DM in older adults,^{5,14,15} we discuss in this review how to deliver, with a multidisciplinary approach, the best benefit from advanced diabetes therapies and technologies to older adults with T2DM according to each patient profile.

Methods

A systematic literature search was performed on MEDLINE (PubMed) to identify clinical studies (either observational or interventional), qualitative studies, systematic reviews/meta-analyses, literature reviews, position statements, expert consensus, and guidelines describing the management of T2DM in older adults. The used keywords were: (“diabetes” OR “diabetic”) AND (“older” OR “elderly”) AND (“management” OR “care”). Only studies published in English within the last 10 years (2013–2023) were included in the search. We also manually screened the reference lists of the included studies.

Patient Profiles and Glycemic Goal-Setting

T2DM management in older adults is complicated by multiple factors, which can be additive (Figure 1). Approximately 60% of older adults with diabetes have a minimum of one comorbid chronic condition, while up to 40% have four or more comorbid conditions.¹⁶ The population of older adults with T2DM is at an increased risk of traditional microvascular and macrovascular T2DM-related complications, in particular chronic kidney disease (CKD) and cardiovascular disease.^{17,18} Moreover, a U-shaped relationship between hemoglobin A1c (HbA1c) and all-cause mortality has been established in older adults. Mortality rate is higher at threshold HbA1c values below 6.5% (48 mmol/mol) and above 8.5–11% (69–97 mmol/mol).^{19,20} In the French GERODIAB prospective, observational study which enrolled 987 patients with T2DM aged 70 years or more and followed over 5 years, increased HbA1c levels ($\geq 8.6\%$ or ≥ 70 mmol/mol) were significantly associated with increased mortality, even in individuals with preserved functional abilities.¹⁹

Older adults with T2DM are also at a greater risk than other older adults for several adverse conditions, such as sarcopenia, bone loss, frailty, urinary incontinence, depression, cognitive impairment, and falls resulting in injury.⁵ In addition, older adults with T2DM have an increased risk of malnutrition as a result of changes in taste and smell, dysphagia, inadequate dental health, gastrointestinal problems, anorexia, cognitive impairment, and/or depression.¹⁵ Older adults are as well increasingly susceptible to hypoglycemia due to the gradual age-related decrease in β -adrenergic receptor function, particularly if they are treated with insulin and/or insulin secretagogues (ie, sulfonylureas and glinides).¹⁰ Dementia and cognitive impairment further put older adults with T2DM at higher risk of severe hypoglycemia due to their inability to identify or report hypoglycemia symptoms to caregivers.²¹ In turn, caregivers may not recognize hypoglycemia in the population of older adults with T2DM, given the lack of adrenergic alarm symptoms, such as sweating, palpitations, and tremors.^{12,21}

Overall, given the high heterogeneity of the population of older adults with T2DM and the heterogeneity of the individual disease course, profiling patients is essential for better personalized management in order to avoid harm and maximize treatment benefits. Accordingly, several scientific societies, including the American Diabetes Association (ADA),⁵ the Endocrine Society,¹⁵ and the International Diabetes Federation (IDF),¹⁴ have categorized older adults into

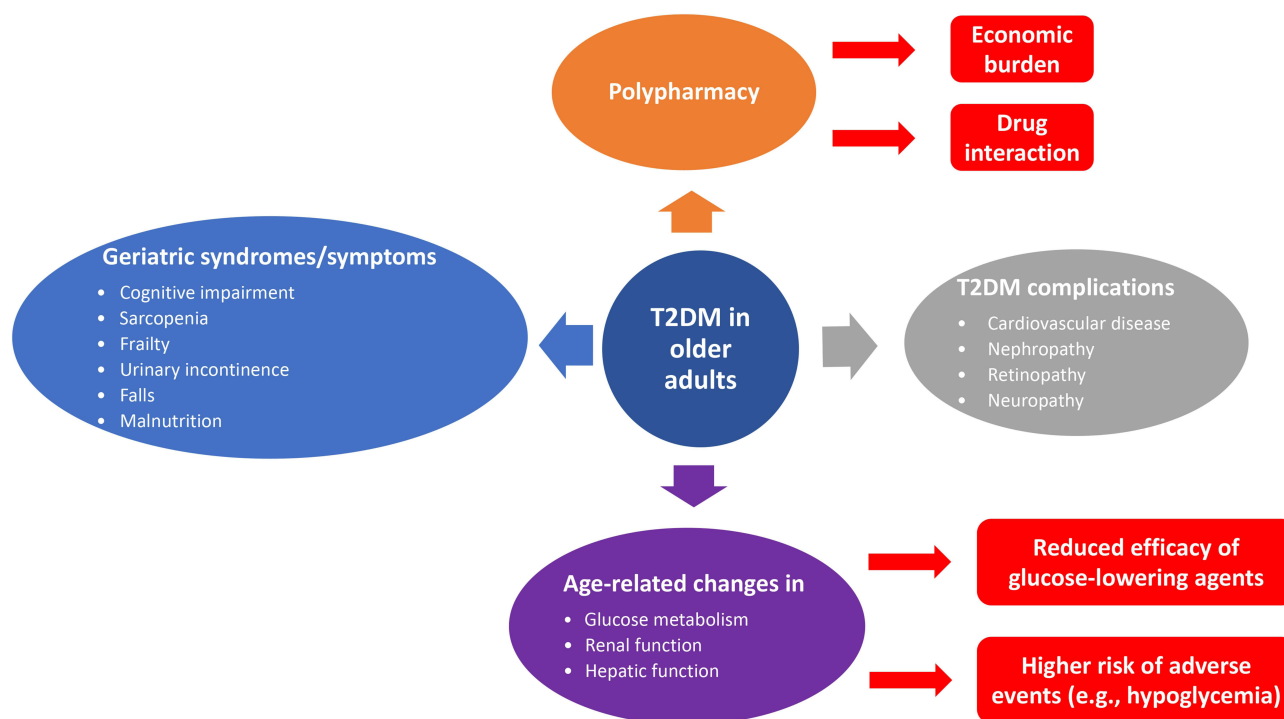


Figure 1 Challenges in the management of type 2 diabetes mellitus (T2DM) in older adults.

three patient groups (ie, good health, intermediate health, and poor health) based on their functional status, cognitive status, comorbidities, and life expectancy to optimize glycemic goal-setting (Table 1). Glycemic target recommendations provided by these different scientific societies are overall consistent.^{5,14,15} In short, older adults with good health, who are functionally and cognitively intact and can be expected to live long enough (eg, >10 years), should receive diabetes care achieving glycemic goals developed for younger adults (HbA1c <7.0–7.5% [53–58 mmol/mol]).^{5,14} The HbA1c target is raised to <8.0–8.5% (64–69 mmol/L) in older adults with intermediate health, who are functionally dependent or have multiple coexisting chronic illnesses or cognitive impairment or dementia. For patients with poor health, who have an end-stage chronic illness and are receiving palliative and/or end-of-life care, reliance on HbA1c should be avoided and glucose control decisions should prioritize the prevention of both hypoglycemia and symptomatic hyperglycemia (Figure 2).^{5,14} Interestingly, a recent national physician survey from the United States found that physicians tend to select more aggressive HbA1c targets than recommended for older adults with intermediate or poor health.²² This finding highlights the need to increase clinicians' comfort with guideline-recommended HbA1c targets for older patients with T2DM.²²

Although patient categorization by society guidelines can facilitate clinical decision-making in older adults with T2DM, it also omits certain geriatric considerations of interest, such as the patient's history and risk of hypoglycemia as well as diabetes duration. In a cross-sectional analysis performed in 1288 adults with diabetes aged ≥ 65 years using data from the National Health and Nutrition Examination Survey, over 50% of older adults had an HbA1c level <7.0% (53 mmol/mol) while being treated with hypoglycemia-associated drugs (insulin and/or sulfonylureas), regardless of their functional status.²³ Having a safe lower limit for HbA1c level may thus be helpful in patients treated with insulin and insulin secretagogues.

Clinical practice guidelines also do not take into account T2DM duration when establishing glycemic goals in older adults.^{5,14,15} However, HbA1c levels significantly rise with the duration of diabetes.²⁴ Compared to older adults with new-onset T2DM, those with long-standing T2DM tend to develop more diabetic complications (eg, CKD and retinopathy) and are at a higher risk of hypoglycemia, as they are more likely to be treated with insulin and for a longer

Table 1 Glycemic Targets in Older Adults (≥65 Years) with Type 2 Diabetes

American Diabetes Association (2023)⁵			
Health status	HbA1c goal	Fasting or pre-prandial glucose	Bedtime glucose
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	<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)
Complex/intermediate (≥3 coexisting chronic illnesses* or ≥2 instrumental ADL [€] impairments or mild-to-moderate cognitive impairment)	<8.0% (64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L)
Very complex/poor health (long-term care or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or ≥2 ADL [€] impairments)	Avoid reliance on HbA1c [¶]	100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)
Endocrine Society (2019)¹⁵			
Health category	HbA1c goal	Fasting glucose	Bedtime glucose
Good health (no comorbidity or 1–2 comorbidities* with no ADL [€] impairments)	<7.5% (58 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	90–180 mg/dL (5.0–10.0 mmol/L)
Intermediate health (≥3 comorbidities and/or any of the following: mild cognitive impairment, early dementia, ≥2 instrumental ADL [€] impairments)	<8.0% (64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L)
Poor health (end-stage medical condition** or moderate-to-severe dementia or ≥2 ADL [€] impairments or residence in a long-term facility)	<8.5% (69 mmol/mol)	100–180 mg/dL (5.6–10.0 mmol/L)	110–250 mg/dL (6.1–13.9 mmol/L)
International Diabetes Federation (2017)¹⁴			
Functional category	HbA1c goal		
Functionally independent (no impairments of ADLs and receiving none or minimal caregiver support)	<7.0–7.5% (53–58 mmol/mol)		
Functionally dependent (impairments of ADL and requiring additional medical and social care) Subcategory A: Frail Subcategory B: Dementia	<7.0–8.0% (53–64 mmol/mol)		
	<8.5% (69 mmol/mol)		
End of life care	Avoid symptomatic hyperglycemia		

Notes: *Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, heart failure, depression, emphysema, falls, hypertension, incontinence, chronic kidney disease, myocardial infarction, and stroke. **The presence of a single end-stage chronic illness, such as stage 3–4 heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy. [€]Activities of daily living (ADLs) include bathing, dressing, eating, toileting, and transferring, and instrumental ADLs include preparing meals, shopping, managing money, using the telephone, and managing medications. [¶]Glucose control decisions should be based on avoiding hypoglycemia and symptomatic hyperglycemia. [§]The glycemic targets set by the Endocrine Society¹⁵ vary according to the use of medications that may cause hypoglycemia (eg, insulin and sulfonylureas).

duration.²⁵ Of note, those who newly develop T2DM at an old age are more likely to have near normal fasting glucose levels but are more prone to experience postprandial hyperglycemia.²⁵

Overall, we believe that for each individual patient, both lower and upper bounds of HbA1c should be set to balance risks and benefits of glucose-lowering treatment, with the main therapeutic objective of avoiding symptomatic hyperglycemia and hypoglycemia. We also believe that target HbA1c range should be regularly reevaluated on an individual basis, with the aim to deliver comprehensive diabetes care rather than a dichotomous model of care (ie, good or poor glycemic control). It is however important to mention that HbA1c measurement may not be accurate in many conditions that are frequently encountered in old age. These include anemia and other conditions that may alter red blood cell turnover, such as advanced CKD and hemodialysis, gastrointestinal bleeding, valvular heart disease, recent blood loss or transfusion, or erythropoietin therapy.^{5,15} Hence, in these situations, self-monitoring of blood glucose (SMBG) using a fingerstick and/or continuous glucose monitoring (CGM) measurement should be systematically proposed as an alternative to HbA1c to guide therapeutic decisions.¹⁵

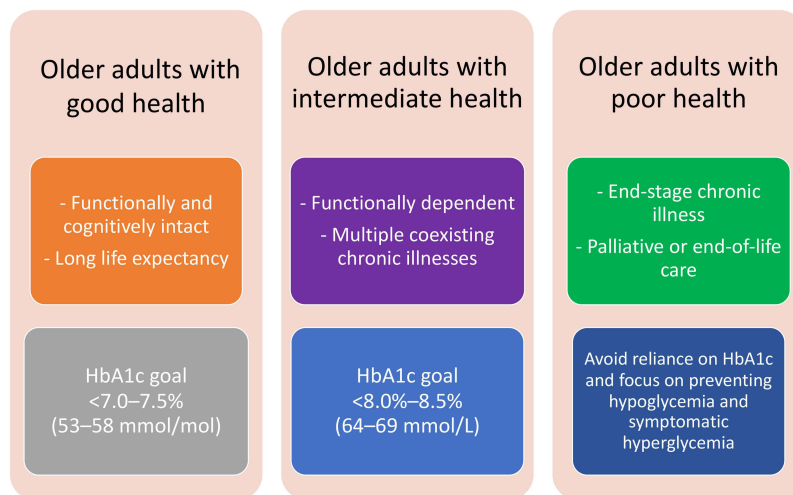


Figure 2 Hemoglobin A1c (HbA1c) goals according to patient profiles of older adults with type 2 diabetes.

Non-Pharmacological Management of T2DM in Older Adults

Lifestyle modifications play an initial role in the effective management of T2DM (Figure 3).⁵ Multi-component lifestyle interventions, such as physical activity and adopting optimal nutrition practices that include sufficient protein intake, can potentially decrease mobility impairments, improve fitness, and reduce HbA1c levels and systolic blood pressure among older adults with T2DM.^{26–28}

Malnutrition and physical inactivity have also been found to be common risk factors for cognitive impairment and frailty.²⁹ Therefore, a healthy dietary pattern consisting of optimal energy intake (of approximately 30 kcal/kg of body weight/day), high intake of protein (of 1.2–1.5 g/kg of body weight/day), vegetables, and fish, including vitamin D and omega-3 fatty acids, and low intake of meat, refined grains, sugar, and snacks could be an important dietary strategy to prevent frailty, cognitive decline, and mortality in older people with T2DM.²⁹ Similarly, clinical practice guidelines by the ADA encourage regular exercise, including aerobic activity, weight-bearing exercise, and/or resistance training, in all older adults with T2DM who can safely engage in such activities.⁵ Indeed, not only does exercise improve insulin resistance, inflammation, and oxidative stress associated with impaired cognition, but it has also been shown to reduce glycemic variability in individuals with obesity as well as T2DM or impaired glucose tolerance.^{28–30}

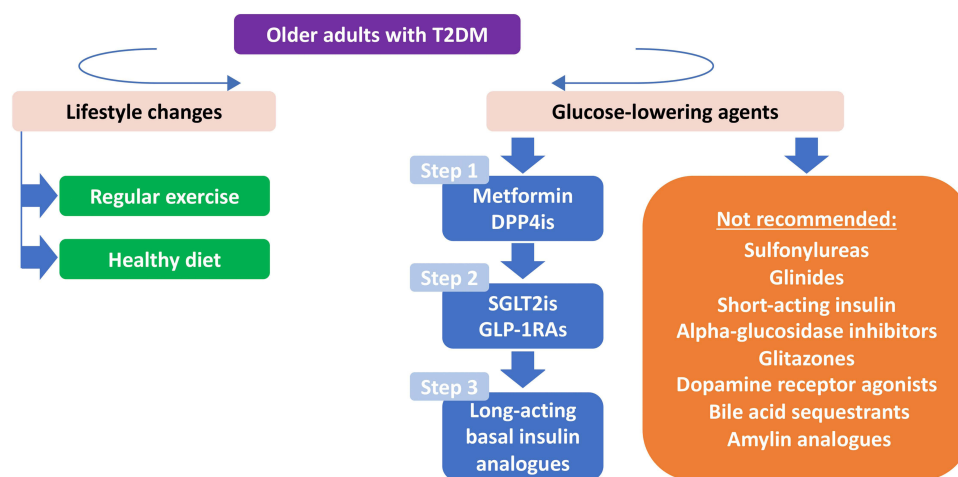


Figure 3 Management algorithm of type 2 diabetes mellitus (T2DM) in older adults.

Abbreviations: DPP4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

Overall, diet and physical activity represent the first step in the management of diabetes. Hence, making informed choices regarding what older adults with T2DM eat and how they stay active can have a profound impact on glycemic control and overall health.

Pharmacological Management of T2DM in Older Adults

Both patient-specific and drug-specific characteristics determine which glucose-lowering agents are appropriate for an older individual with T2DM. These include comorbidities such as atherosclerotic cardiovascular disease (ASCVD), CKD, and heart failure; hypoglycemia risk; cognitive function; functional status; effect of glucose-lowering agents on body weight and their associated safety profile; individualized glycemic goals; patient preferences; and treatment cost.⁵ Overall, a close follow-up and repeated patient profile assessments and treatment adjustments (for instance in case of treatment non-adherence, hospitalization, or treatment for cancer) are key in the management of older adults with T2DM.

Various oral and injectable glucose-lowering agents are available for the treatment of T2DM in older adults (Table 2). When initiating glucose-lowering therapy in the population of older adults with T2DM, the principle of “start low, go slow” applies.³¹ Overall, most glucose-lowering agents can be safely used for the treatment of T2DM in older persons, with some considerations according to patient profiles (Table 3). In this respect, due to a high risk of hypoglycemia, insulin secretagogues (sulfonylureas or glinides) and/or short-acting insulin should be avoided in older adults with T2DM, or, in the absence of alternative treatment strategies, managed with extreme caution (ie, adoption of low doses, reinforced blood glucose monitoring).³² Alpha-glucosidase inhibitors should also not be administered in older adults with T2DM because of relatively low efficacy and abdominal adverse events (AEs) of bloating, flatulence, and diarrhea.³³ In addition, glitazones should be avoided, as they might lead to fluid retention, which could precipitate or exacerbate heart failure. Pioglitazone is also associated with an increased risk of bone fractures, which detracts from its use in frail patients.³³

Patient Profile-Oriented Management

In functionally independent older adults with good health, given their longer remaining life expectancy (>10 years), the same treatment principles should be applied as in younger patients with T2DM, including the use of advanced technologies such as novel insulin delivery systems. Practitioners should nevertheless be mindful of the risk of hypoglycemia in these individuals when adding in glucose-lowering therapies, as the consequences of hypoglycemia may be just as significant in the functionally independent as the functionally dependent older adult with diabetes.

In less fit patients with intermediate or poor health, glucose-lowering treatment regimens (especially insulin) should be kept as simple as possible to reduce polypharmacy and decrease both disease and drug burden as well as complexity of medication regimens.⁵ A systematic review, of 10 observational cohort and interventional studies conducted in a total of 26,925 older adults (≥ 65 years) with T2DM and with or without comorbidities such as ASCVD, CKD or dementia, reported no deterioration in HbA1c levels, hypoglycemic episodes, falls, or hospitalizations following deintensification (defined as “complete withdrawal, discontinuation, reducing dosage, conversion, or substitution of at least one glucose-lowering medication”).³⁴ A single-arm, interventional study performed in older adults (≥ 65 years) with T2DM additionally found that insulin regimen simplification by switching from multiple-dose insulin regimens to once-daily insulin glargine combined or not with non-insulin agents can lower hypoglycemia risk and diabetes-related distress without compromising glycemic control.³⁵ Treatment regimen simplification can also offer practical benefits such as reducing the frequency of administration, minimizing the need for frequent blood glucose checks, and eliminating the requirement for complex calculations like sliding-scale insulin or insulin-carbohydrate ratio calculations.⁵

Although clinical practice guidelines emphasize the importance of simplified treatment regimens in older adults, such guidance is often uncertain.^{5,14,15} However, to be mindful of patients’ quality of life, guidelines recommend in functionally dependent older people the avoidance or discontinuation of agents that might cause nausea or gastrointestinal disturbance as well as excess weight loss.^{5,14} It is important to mention that periodic assessments should be conducted for each individual to evaluate their eligibility for treatment simplification, since simplification may not be appropriate for some patient profiles such as hospitalized individuals, those with severe insulin deficiency, or those at higher risk of occurrence or progression of micro- or macrovascular complications.³⁶

Table 2 Advantages and Disadvantages of Glucose-Lowering Agents in Older Adults (≥ 65 Years) with Type 2 Diabetes

Medication	Route	Advantages	Disadvantages
Metformin	Oral	<ul style="list-style-type: none"> - Low hypoglycemia risk - Weight neutral - Low cost 	<ul style="list-style-type: none"> - To use with caution in those with impaired hepatic function or heart failure due to increased risk of lactic acidosis - GI side effects (nausea, diarrhea) - Contraindicated if eGFR < 30 mL/min/1.73 m²
Sulfonylureas (eg, glipizide, gliclazide, glimepiride, glibenclamide)	Oral	<ul style="list-style-type: none"> - Rapidly effective 	<ul style="list-style-type: none"> - Hypoglycemia risk - Controversial cardiovascular safety (mainly for glibenclamide) - Interacts with certain drugs in older people (eg, non-selective beta-blockers, salicylates, NSAIDs, ACE inhibitors)
Glinides (eg, repaglinide, nateglinide)	Oral	<ul style="list-style-type: none"> - Rapidly effective 	<ul style="list-style-type: none"> - Hypoglycemia risk - Three times per day dosing - Interacts with certain drugs in older people (eg, non-selective beta-blockers, salicylates, NSAIDs, ACE inhibitors)
DPP-4 inhibitors (eg, sitagliptin, alogliptin, linagliptin, saxagliptin, vildagliptin)	Oral	<ul style="list-style-type: none"> - Low hypoglycemia risk - Weight neutral 	<ul style="list-style-type: none"> - Increased risk of hospitalization for heart failure with specific DPP-4 inhibitors (saxagliptin and alogliptin)
SGLT-2 inhibitors (eg, empagliflozin, canagliflozin, dapagliflozin)	Oral	<ul style="list-style-type: none"> - Low hypoglycemia risk - Cardiovascular benefits, most notably on heart failure hospitalization - Nephroprotection - Weight loss mainly due to visceral and subcutaneous adipose tissue loss (as opposed to lean body mass loss), which could benefit older adults with sarcopenic obesity 	<ul style="list-style-type: none"> - Contraindicated if eGFR < 20 mL/min/1.73 m² - Glucose-lowering efficacy diminishes with declining renal function - Risk of orthostatic hypotension (falls) especially if concomitant use of diuretics - Glucosuric effect associated with risk of urinary tract infections and dehydration
Glitazones (eg, pioglitazone)	Oral	<ul style="list-style-type: none"> - Low hypoglycemia risk - Improves lipid profile - Antiatherogenic effects 	<ul style="list-style-type: none"> - Risk of osteoporosis and fractures - Fluid retention and weight gain
Alpha-glucosidase inhibitors (eg, acarbose)	Oral	<ul style="list-style-type: none"> - Low hypoglycemia risk - Improves postprandial hyperglycemia 	<ul style="list-style-type: none"> - GI side effects (bloating, flatulence, diarrhea) - Relatively low efficacy
Dopamine receptor agonists (eg, bromocriptine mesylate)	Oral	<ul style="list-style-type: none"> - Low hypoglycemia risk - Improves postprandial hyperglycemia 	<ul style="list-style-type: none"> - Relatively low efficacy - Several drug interactions noted with bromocriptine mesylate - Limited clinical experience in managing diabetes - GI side effects (mainly nausea)

(Continued)

Table 2 (Continued).

Medication	Route	Advantages	Disadvantages
Bile acid sequestrants (eg, colesevelam)	Oral	<ul style="list-style-type: none"> - Lowers LDL cholesterol - Low hypoglycemia risk 	<ul style="list-style-type: none"> - Relatively low efficacy - Increases triglyceride levels - GI side effects (bloating, constipation)
Insulin (eg, basal insulin analogues such as insulin detemir, glargine, degludec)	Subcutaneous	<ul style="list-style-type: none"> - Rapidly effective - Anabolic effect 	<ul style="list-style-type: none"> - Hypoglycemia risk - Injection requires good visual acuity and motor skills
GLP-1 receptor agonists (eg, lixisenatide, liraglutide, exenatide, dulaglutide, semaglutide)	Subcutaneous (with semaglutide also available orally)	<ul style="list-style-type: none"> - Low hypoglycemia risk - Cardiovascular benefits, most notably on stroke - Once-weekly administration possible with exenatide, dulaglutide, or semaglutide, which may improve patient adherence 	<ul style="list-style-type: none"> - Weight loss, which is not appropriate in frail patients, as it may result in sarcopenia - GI side effects (nausea, diarrhea, vomiting)
GIP/GLP-1 receptor co-agonists (eg, tirzepatide)	Subcutaneous	<ul style="list-style-type: none"> - Low hypoglycemia risk - Cardiovascular benefits - Once-weekly administration, which may improve patient adherence 	<ul style="list-style-type: none"> - Substantial weight loss, which is not appropriate in frail patients, as it may result in sarcopenia - GI side effects (nausea, diarrhea, constipation)
Fixed-ratio combinations of basal insulin and GLP-1 receptor agonists (eg, insulin degludec/liraglutide, insulin glargine/lixisenatide)	Subcutaneous	<ul style="list-style-type: none"> - Enhanced glycemic control - Offers simplification of treatment regimens 	<ul style="list-style-type: none"> - GI side effects (nausea, diarrhea, vomiting) - Hypoglycemia risk
Amylin analogues (eg, pramlintide)	Subcutaneous	<ul style="list-style-type: none"> - Improves postprandial hyperglycemia 	<ul style="list-style-type: none"> - Weight loss, which is not appropriate in frail patients, as it may result in sarcopenia - Hypoglycemia risk - Relatively low efficacy - GI side effects (nausea, vomiting)

Abbreviations: ACE, angiotensin-converting enzyme; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1; LDL, low-density lipoprotein; NSAID, non-steroidal anti-inflammatory drug; SGLT-2, sodium-glucose co-transporter-2.

Table 3 Treatment Considerations According to Patients' Health Status

Health Status	Treatment Considerations
Good health/functionally independent	<ul style="list-style-type: none"> - Metformin is the first-line medication if not contraindicated - If metformin is contraindicated (eg, advanced renal impairment), a DPP-4 inhibitor should be considered if available and affordable - To reduce the risk of hypoglycemia, avoid using sulfonylureas and glinides - Patient-specific factors determine which agents are appropriate for dual or triple therapy, if indicated, to achieve glycemic control. For instance, in case of ASCVD or high risk of ASCVD, the use of GLP-1 receptor agonists or SGLT-2 inhibitors may be beneficial - Include an individualized glycemic monitoring plan (using SMBG and/or CGM) to optimize decisions regarding medication adjustments as well as lifestyle changes
Intermediate health/functionally dependent	<ul style="list-style-type: none"> - Same principles as for those with good health - Glucose-lowering treatment regimens should be kept as simple as possible to decrease pill burden and complexity of medication regimens - Use of GLP-1 receptor agonists and SGLT-2 inhibitors may be problematic, as their weight loss effect can be detrimental in the frail person - Since insulin may provide anabolic benefits, the use of a simplified insulin regimen with a low hypoglycemia risk may be considered (eg, long-acting basal insulin analogues such as insulin glargine, detemir, or degludec) - CGM should be limited to detect asymptomatic and nocturnal hypoglycemia, especially in those on insulin regimen
Poor health/end-of-life care	<ul style="list-style-type: none"> - Treatment goals are to provide comfort, avoid hypoglycemia, and symptomatic hyperglycemia, and preserve remaining quality of life - Treatment strategies should be simplified and therapies deintensified for patients nearing the end of life - Since insulin may provide anabolic benefits, the use of a simplified insulin regimen with a low hypoglycemia risk may be considered (eg, long-acting basal insulin analogues) - CGM should only be considered under special circumstances (eg, commencement of corticosteroids) and when the danger of hypoglycemia is very high (eg, significant nutritional problems)

Abbreviations: CGM, continuous glucose monitoring; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon like peptide-1; SGLT-2, sodium-glucose co-transporter-2; SMBG, self-monitoring of blood glucose.

In the particular case of older adults at the end of life receiving palliative medicine or hospice care, individuals are free to decline testing and treatment, and healthcare professionals may consider discontinuing treatment and limiting diagnostic testing, such as reducing the frequency of blood glucose monitoring.⁵ For dying patients with T2DM, it may be a reasonable approach to discontinue all glucose-lowering medications, as these individuals are unlikely to have any oral intake. If needed, long-acting basal insulin can be implemented, since it provides anabolic benefits.^{5,14}

While individualization of therapy is desirable, availability, cost, and local prescribing regulations are the primary factors that determine therapeutic choice in real-world clinical practice.¹⁴

Metformin and Dipeptidyl Peptidase-4 Inhibitors (DPP4is)

In both younger and older adults with T2DM, metformin is unanimously recommended by clinical practice guidelines as the preferred first-line therapy because of its low cost, low potential for hypoglycemia, and its high glycemic efficacy.^{5,14,15} Nevertheless, metformin should be cautiously used in patients with renal dysfunction (contraindicated in patients with an estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m²) or impaired hepatic function or heart failure because of the increased risk of lactic acidosis.^{5,15,21} For patients with contraindications and/or intolerance to metformin, dipeptidyl peptidase-4 inhibitors (DPP4is) can be given as first-line therapy, as they have few AEs and a minimal risk of hypoglycemia, and can be safely used in individuals with CKD. However, their relatively high cost may present a barrier for certain older adults, and DPP4is may not be easily available in many countries.^{5,14} Metformin is also known to cause gastrointestinal AEs such as nausea and diarrhea, limiting its use in older adults who might be affected by malnutrition and/or reduced oral intake (due to dysphagia

for instance).^{5,21} Healthcare providers could however choose an extended-release formulation of metformin to lower the risk of gastrointestinal intolerance.²¹

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs) and Sodium-Glucose Co-Transporter-2 Inhibitors (SGLT2is)

Because T2DM slowly worsens over time, adding glucose-lowering medications to first-line therapy may be necessary to achieve adequate glycemic control. However, the optimal sequence for adding drugs after metformin remains uncertain in older adults.¹⁵ Sodium-glucose co-transporter-2 inhibitors (SGLT2is) or glucagon-like peptide-1 receptor agonists (GLP-1RAs) are reasonable second agents for older adults with established or at increased risk of ASCVD, given their demonstrated cardiovascular benefits and low hypoglycemia risk.^{5,14,15}

In a meta-analysis of 11 randomized controlled trials (RCTs) in older patients (≥ 65 years) with T2DM, both GLP-1RAs and SGLT2is significantly reduced major adverse cardiovascular events (MACE) by 14% for GLP-1RAs (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.80–0.92) and by 13% for SGLT2is (HR, 0.87; 95% CI, 0.74–1.01).³⁷ Of particular relevance to the older population, stroke, a component of MACE, was significantly reduced by GLP-1RAs (HR, 0.82; 95% CI, 0.68–0.98), and SGLT2is significantly reduced heart failure hospitalization (HR, 0.62; 95% CI, 0.51–0.76).³⁷ Growing evidence also suggests that GLP-1RAs have potential neuroprotective effects, which can be useful in the treatment of neurodegenerative diseases, especially Parkinson's disease and Alzheimer's disease.³⁸ However, caution should be exercised regarding the use of SGLT2is and GLP-1RAs in individuals older than 80 years, due to the lack of both RCT data and real-world data in this patient population.

Since both GLP-1RAs and SGLT2is promote weight loss, including lean mass loss, practitioners should consider avoiding them in frail older adults or in those who may be at increased risk of anorexia or malnutrition.¹⁵ GLP-1RAs are also associated with nausea, vomiting, and diarrhea. To minimize the gastrointestinal AE profile of GLP-1RAs, healthcare providers should initiate GLP-1RAs at a low dosage and gradually increase the dose to reach the maximal tolerated dose.^{5,21} SGLT2is should also be cautiously used in frail patients due to the risk of plasma volume reduction and potential falls resulting from hypotension.³⁹ The use of SGLT2is in older adults is further restricted by AEs such as dehydration, increased thirst and polyuria, an increased risk of genital and urinary tract infections, and reduced glucose-lowering effectiveness in patients with preexisting CKD.⁸ Plasma volume status and kidney function (serum creatinine with eGFR) should therefore be assessed prior to starting an SGLT2i and periodically thereafter. In the frail older adult, DPP4is thus remain a convenient add-on treatment alternative option to metformin due to their excellent safety profile.

All GLP-1RAs, with the exception of oral semaglutide, are injectable agents, which require visual, motor, and cognitive skills for appropriate administration.⁵ There are however once-weekly options, namely exenatide, dulaglutide, and semaglutide, that facilitate adherence and could be a good treatment option in patients with cognitive impairments or depression, particularly if at increased risk of hypoglycemia due to the use of insulin or insulin secretagogues, since they can be administered conveniently by caregivers.³⁹ Indeed, it has been shown that when older patients with T2DM develop cognitive dysfunction, they are significantly less likely to be involved in diabetes self-care and are at increased need of assistance.⁴⁰

Insulin Therapy

In patients with long-standing T2DM, insulin should be administered as add-on therapy, particularly in case of persistent hyperglycemia on oral glucose-lowering therapies. Interestingly, in adults aged ≥ 65 years with uncontrolled diabetes, early treatment with insulin glargine resulted in better glycemic control and less hypoglycemia than continuing to titrate oral agents such as insulin secretagogues.⁴¹ Insulin therapy in older adults should be tailored according to individualized glycemic targets, level of functional dependency, and supportive care availability.^{5,42}

The most convenient and simple insulin regimen to use in older adults with T2DM is a once-daily injection of one of the long-acting basal insulin analogues (insulin detemir, glargine, or degludec), which are associated with minimal AEs, and more specifically with a lower risk of hypoglycemia than neutral protamine Hagedorn (NPH) insulin.^{5,14,43} Supporting this therapeutic choice, initiation of insulin glargine or detemir was associated with an approximately 30%

lower risk of emergency department visits or hospitalizations for hypoglycemia in adults aged ≥ 65 years with T2DM, as compared to NPH insulin.⁴⁴ It is also preferable to administer long-acting basal insulin in the morning, since older adults (≥ 65 years) with diabetes tend to have a higher incidence of postprandial hyperglycemia compared with fasting hyperglycemia than younger adults (< 65 years) at all HbA1c levels.⁴⁵ To minimize the risk of hypoglycemia, long-acting basal insulin should be titrated gradually, and its dosage should be adjusted on a weekly basis until the desired fasting blood glucose target is reached.²¹

Recently, once-weekly basal insulin analogues (eg, insulin icodex) have shown glucose-lowering effects and a safety profile similar to those of once-daily basal insulin analogues,⁴⁶ and could hence become another therapeutic advance that may ease the burden of self-care, once available. However, the efficacy and safety of once-weekly basal insulin analogues in the older patient population still need to be demonstrated.

Of note, due to its anabolic effects, insulin therapy is the preferred glucose-lowering therapy in patients with severe malnutrition.⁴³ The use of complex insulin schemes should however be avoided, if possible, due to the increased risk of overall and severe hypoglycemia associated with prandial insulin injections in the context of older patients with diabetes.³⁵

Newer insulin delivery devices, such as insulin pumps and smart insulin pens, are being more frequently used in older adults with diabetes to enhance their quality of life and lower the risk of hypoglycemia. Indeed, these devices can ease the load of self-care and make older adults feel more secure.⁴⁷

Smart insulin pens are connected insulin delivery devices that can track insulin dosing through a smart phone app.⁴⁸ Although some older adults with cognitive decline may encounter challenges when operating insulin pens, particularly when it comes to changing cartridges, Bluetooth-enabled pens can be used to track missed or extra doses. The tracking provided by the devices is useful in patients with cognitive impairment, as it can be used by caregivers, whether aids, nurses, or family members, to remind patients to take their insulin or eat meals on time.⁴⁷ Indeed, in a small cross-sectional study performed in both younger (≤ 35 years) and older (≥ 65 years) adults with diabetes on two or more insulin injections per day, the use of Bluetooth-enabled insulin pens was shown to accurately detect any divergence from insulin prescriptions.⁴⁹ Further dedicated studies evaluating smart insulin pens in the population of older adults with T2DM are warranted.

Insulin pumps deliver a continuous supply of insulin throughout the day. The majority of insulin pumps use tubing to deliver insulin through a cannula, whereas some pumps, known as patch pumps, attach directly to the skin without the need for tubing. The use of insulin pumps offers convenience to older adults by eliminating the need to carry multiple insulin pens.⁴⁷ Supporting the use of such devices in selected patients, the OpT2mise RCT compared insulin pump treatment with multiple daily injections of insulin in individuals with T2DM aged up to 75 years who had not responded to a basal-bolus regimen after active insulin titration.⁵⁰ Insulin pump treatment notably improved glycemic control independently of diabetes duration, body mass index, and cognitive ability, and was associated with a low hypoglycemia risk.⁵⁰ Despite these positive results, the use of insulin pumps in older adults, but also in younger adults, may be limited by the inability to remember the multiple steps to change tubing and cannula, difficulty to see insulin pump screens due to their small size and the lack of magnification abilities, and the risk of diabetic ketoacidosis in insulin-deficient patients.⁴⁷

Overall, if the use of an advanced insulin delivery system is validated in an older patient, periodic assessment of cognitive and functional status, as well as overall health, should be performed to continually re-evaluate the benefits and potential burden of this technology. Guidelines for the use of insulin administration systems in older adults with T2DM are still needed, along with educational material for the clinicians caring for them and the caregivers helping them at home.⁴⁷ There is also a need for solid research data assessing the efficacy and safety of insulin delivery systems in the population of older patients with diabetes.

T2DM Treatment Monitoring in Older Adults

Although there are limited clinical data to guide T2DM treatment monitoring in older adults, it should be tailored to individual glycemic targets, functional status, and patient characteristics (eg, vision, hearing, manual dexterity, comorbidities, and social and financial situation). Guidelines by the Endocrine Society recommend that in patients with diabetes aged ≥ 65 years who are treated with insulin, frequent SMBG and/or CGM should be performed in addition to HbA1c measurement (Figure 4).¹⁵

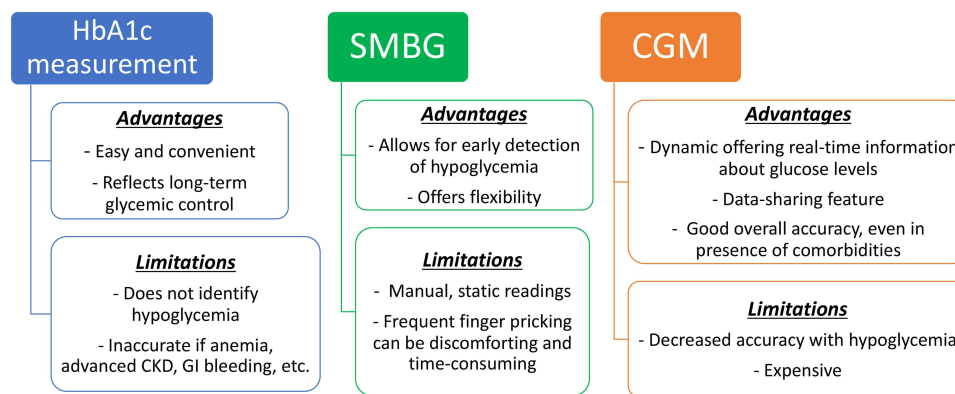


Figure 4 Glycemic monitoring in older adults with type 2 diabetes.

Abbreviations: CGM, continuous glucose monitoring; CKD, chronic kidney disease; GI, gastrointestinal; HbA1c, hemoglobin A1c; SMBG, self-monitoring of blood glucose.

Even though HbA1c measurement serves as an appropriate means to assess overall glycemic control, it does not aid in identifying hypoglycemia.¹⁵ However, this is particularly important in the aging population, since both hypoglycemia and hyperglycemia (dysglycemia) may increase the risk of frailty in older people with T2DM.⁵¹ Older adults with T2DM also display distinct glucose patterns, characterized by a relatively higher incidence of postprandial hyperglycemia compared to fasting hyperglycemia.¹⁵ CGM can be a practical tool to safely assess glycemic profiles and decreasing glucose variability in older adults, especially for those on multiple daily doses of insulin.^{5,15} In contrast to SMBG that is a static measurement providing an instantaneous glucose level, CGM is a dynamic measurement that not only provides real-time glucose values but also offers information about fluctuations and trends in glucose levels over time.⁵²

The benefits of CGM have been demonstrated in both older adults with type 1 and type 2 diabetes. In the WISDM RCT including adults aged ≥ 60 years with type 1 diabetes, CGM for 6 months compared with standard blood glucose monitoring was associated with a reduced time spent in hypoglycemia by approximately 27 minutes per day.⁵³ Similarly, CGM proved to be useful for investigating hypoglycemia and glycemic variability in the IMPERIUM study performed in moderately ill and/or frail older (≥ 65 years) individuals with inadequately controlled T2DM.⁵⁴ In the MOBILE RCT comparing CGM to SMBG in adults with T2DM treated with basal insulin without prandial or bolus insulin, improvement in key glycemic outcomes, including time-in-range and less time in hyperglycemia, was observed with CGM compared with SMBG in participants ≥ 65 years old (mean \pm standard deviation age of 69 ± 4 years), and was comparable with the treatment outcomes observed in younger participants.⁵⁵

A recent analysis of a heterogeneous non-critically ill inpatient population with diabetes on insulin therapy demonstrated good overall accuracy of CGM, even in the presence of comorbidities such as impaired renal function, cardiovascular and respiratory illnesses, and mild-to-moderate anemia.⁵⁶ Nonetheless, CGM accuracy decreased with hypoglycemia (< 70 mg/dL or 3.9 mmol/L) and severe anemia (hemoglobin < 7.0 g/dL or 4.3 mmol/L).⁵⁶ Other factors that can potentially compromise the accuracy of CGM measurements include skin edema that might dilute interstitial fluid glucose, vasoconstrictor drugs that might decrease blood flow to the skin and result in a slower shift of glucose from capillaries to the interstitial fluid compartment, and hypotension that could lead to peripheral vasoconstriction and hypoxemia.⁵⁷

To date, despite recent guidelines for the use of technology in diabetes, the optimal utilization of CGM in older adults is still not well-established, highlighting the importance of the development of dedicated guidelines for CGM in the older patient population. Moreover, CGM remains underused in routine clinical practice, as a consequence of logistical, educational, and financial barriers.⁵⁸ Education and behavioral support may equip caregivers with skills to support the use of CGM in older adults with T2DM.⁵⁸

In the context of end-of-life care, the decision regarding the discontinuation or the continuation of glucose monitoring, as well as the choice between CGM devices and fingerstick blood glucose monitoring, must be tailored to individual

preferences. It is also important to consider patient and caregiver preferences, the stage of end-of-life care, and the level of experience of the medical and nursing staff.⁵⁹ The IDF specifies that the threshold for continuing glucose monitoring in patients receiving end-of-life care should be high and only considered under unique circumstances (eg, beginning of corticosteroids known for their hyperglycemic effects) and when the risk of hypoglycemia is specifically high (eg, in case of important nutritional problems).¹⁴ In functionally dependent patients with intermediate health (eg, with multiple comorbidities), the use of CGM is useful to prevent unrecognized hypoglycemia episodes, especially in individuals on insulin regimen or those who have difficulties with fingerstick monitoring.⁴⁷ In fit patients with good health, glycemic monitoring should be considered as an optional component of self-management, especially when there is an agreed purpose for testing (eg, if intensification of pharmacotherapy, modified eating patterns, use of medications causing hypoglycemia such as insulin or insulin secretagogues).¹⁴

During the COVID-19 pandemic, telemedicine has greatly expanded, and the role of CGM in relaying patient data to healthcare providers has been instrumental.⁶⁰ Indeed, there is now an availability to use CGM transmitters connected to glucose sensors transmitting glucose values through Bluetooth connectivity to selected users who can remotely monitor glucose levels on compatible smart devices. This data-sharing feature can be especially helpful to caregivers of frail older adults who struggle with cognitive decline. It also reduces the workload of healthcare providers and adds to quality of diabetes care, especially when patient access to diabetes care facilities is limited.^{47,61} Importantly, the stereotype that older adults are not technology-savvy should be avoided, with assessment on an individual basis of the use of CGM and other telemedicine technologies in older adults. Further longitudinal research data on both short-term and long-term outcomes of older adults with diabetes receiving care through telemedicine is needed.

Multidisciplinary Care in Older Adults

A multidisciplinary patient-centered approach, involving an endocrinologist or diabetes care specialist, a geriatrician, a general practitioner, a dietician or nutritionist, a pharmacist, a physical therapist, and in some cases a home nurse, is important to guarantee high-quality diabetes care and to improve older patients' quality of life.⁶² Effective multidisciplinary teams are also core to the assessment of geriatric syndromes in older adults with T2DM, given that geriatric syndromes are multifactorial and do not fit into distinct disease categories.⁶³ Moreover, geriatric syndromes such as frailty may be difficult to diagnose in clinical practice, particularly since the trajectories and transitional states of frailty in older adults with diabetes have yet to be firmly established.^{42,64,65} Acknowledging that frailty is a multifactor clinical syndrome, multidisciplinary teams can facilitate the implementation of frailty screening in an integrated management approach.⁶⁶ Management of geriatric syndromes in older adults with diabetes should be especially directed by the Comprehensive Geriatric Assessment (CGA), a multidimensional, interdisciplinary evaluation used to assess older patients' medical, psychological, physical functions and social status.⁶⁷

It is particularly crucial that healthcare providers engage in in-depth and open discussions with their patients, when evaluating their personalized care, to increase the likelihood of effectively integrating glucose-lowering treatment into the patient's daily routine.³⁶ Unfortunately, in a qualitative study of 32 adults aged ≥ 60 years with T2DM and other chronic conditions, older adults perceived a general unwillingness from their healthcare providers to treat their multiple-health conditions and to accommodate to their individual care preferences. The limited support and empathy from the healthcare providers may have been attributed to age discrimination.⁶⁸ Patient-reported outcome measures can be a useful tool to inform shared decision-making, by gaining insight into a patient's experience of glucose-lowering treatment and its burden.³⁶

To date, there is a paucity of studies evaluating the effectiveness of a multidisciplinary care model for older adults with T2DM. A five-year, prospective, cohort study, performed in 121,584 Chinese primary care patients with T2DM, evaluated a multidisciplinary, risk-stratified, chronic disease model care and found that compared with usual care, multidisciplinary care led to significantly greater reductions in ASCVD risk by 56.6%, microvascular complications by 11.9%, mortality by 66.1%, specialist attendance by 35.0%, emergency attendance by 41.2%, and hospitalizations by 58.5%.⁶⁹ Geriatric day hospitals (GDHs), usually englobing multidisciplinary teams of physicians, nurses, dieticians, psychologists, physiotherapists, occupational therapists, and social workers, can also allow for a collaboration between the inpatient and community care for older adults with diabetes. Indeed, a prospective cohort study performed in 469

outpatients admitted to a Canadian GDH demonstrated short- and long-term effectiveness of GDH in helping patients reach their individualized outcome targets.⁷⁰ Overall, multidisciplinary care models can improve T2DM treatment outcomes and help prevent or reduce T2DM complications. However, in order to optimize their effectiveness, multidisciplinary teams require robust team structures, dependable communication methods, and high patient engagement.⁷¹

Summary

Given that older adults with diabetes are a highly heterogeneous patient population with unique care needs, their categorization into different patient profiles (ie, good health, intermediate health, poor health) may aid in clinical decision-making when establishing glycemic goals and treatment strategies. Further granularity in assessing each patient profile through interdisciplinary collaboration may also add precision to therapeutic and monitoring decisions. Thus, management of T2DM in older adults should always be tailored, based on comprehensive geriatric and environmental assessments that include ASCVD risk, functional status, hypoglycemic risk and awareness, renal function, body weight, presence of depression and/or cognitive impairment, history of urinary incontinence and/or falls, duration of diabetes, patient preferences, and available care facilities. There are still several areas that deserve further research in older adults with T2DM, including the efficacy and safety of CGM and automated insulin delivery systems, the switch to once-weekly insulin, and the use of supported telemedicine and remote blood glucose monitoring in the oldest-old (≥ 85 –90 years) who particularly require the assistance of others.

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