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REVIEW

Special Considerations When Using GLP-1 Receptor Agonists in the Treatment of Obesity and Diabetes Mellitus Type 2 in Older Adults

Anna Geraldina Pendrey · Jennyfer Alejandra Rivera Sierra · Fernando Alberto Alvarez Lobo · Eblin Jackeline Ríos Herrera · Yolanda María Fernandez Muñoz · Javier Francisco Sevilla Martir

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ABSTRACT

The prevalence of obesity and type 2 diabetes mellitus (T2DM) in the older adult population is rising continuously worldwide, with approximately 40% and 29% of individuals affected in this group, respectively. These conditions have a substantial impact on older adults and are associated with reduced quality of life, increased morbidity, functional decline, and cardiovascular disease. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as an important option for the management of T2DM and obesity. However, special considerations are needed for specific age groups due to risks of adverse effects and increased comorbidity burden. GLP-1 RAs, including tirzepatide, liraglutide, and semaglutide, promote weight loss by suppressing appetite, improving insulin secretion, and delaying gastric emptying. Large clinical trials have supported GLP-1 RAs as an excellent option for reducing glycated hemoglobin and body weight, as well as for reducing major renal and cardiovascular adverse effects; however, evidence in older adults remains limited. Given the health considerations for older adults, weight loss efforts with GLP-1 RAs require cautious approaches, as sarcopenia is a relevant topic in this specific age group. Polypharmacy and side effects also need to be considered when treating an older adult with GLP-1 RA. Overall, GLP-1 RAs represent a valuable and promising treatment option for older adults with T2DM and obesity.

Keywords: Diabetes; Glucagon-like peptide-1 receptor agonists; Obesity; Older adults

A. G. Pendrey (✉) · J. F. Sevilla Martir
Department of Family Medicine, Indiana University School of Medicine, Indianapolis, IN, USA
e-mail: apendrey@iu.edu

J. A. Rivera Sierra · F. A. Alvarez Lobo · E. J. Ríos Herrera
Facultad de Ciencias Médicas, Distrito Central, Universidad Nacional Autónoma de Honduras, Francisco Morazán, Honduras

Y. M. Fernandez Muñoz
Distrito Central, Universidad Católica de Honduras, Francisco Morazan, Honduras

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Key Summary Points

Obesity and type 2 diabetes mellitus are major burdens in older adults; they affect > 40% and 29% of older adults, respectively, and are strongly associated with comorbidities such as cardiovascular disease.

GLP-1 receptor agonists, including semaglutide, tirzepatide, and liraglutide, are used in older adults, with a specific focus on improving metabolic health by enhancing weight loss, improving glycemic control, and protecting the cardiovascular system.

GLP-1 receptor agonists are a good option for the treatment of obesity and T2DM in older adults; nevertheless, in this population, it is important to consider the risk for sarcopenia, malnutrition, gastrointestinal side effects, and polypharmacy.

INTRODUCTION

Globally, the incidence of chronic diseases is increasing, and people's quality of life is being affected. Obesity, a global pandemic, is on the rise, affecting all ages, including older adults. Approximately 42% of people > 65 years old are obese [1]. In this population, it is closely associated with comorbidities, including T2DM, cardiovascular disease, frailty, and cognitive decline. Obesity in older adults requires interprofessional and interdisciplinary management and a careful balance between metabolic benefits and the risks of excessive weight loss, particularly sarcopenia and malnutrition [2].

Against this background, the management of obesity and T2DM has been modified by the advent of GLP-1 RAs. Beyond glucose control, these agents reduce appetite, promote weight loss, delay gastric emptying, and have demonstrated potential cardiovascular and renal benefits. However, older adults remain underrepresented in clinical trials, and their specific risk-benefit profile remains incompletely characterized.

Therefore, the use of GLP-1 RAs in older adults requires an integrated metabolic and functional approach. In this context, therapeutic priorities include preservation of muscle mass, prevention of frailty progression, and maintenance of functional independence, in addition to glycemic control and weight management.

The purpose of this review is to provide evidence on the use of GLP-1 RAs in older adults with obesity and T2DM and their safety and efficacy. The review is conducted to identify strategies that improve the quality of life in older adults and to guide decision-making in primary care and geriatric practice. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

OBESITY AND T2DM: EPIDEMIOLOGY AND IMPACT

Obesity and type 2 diabetes mellitus are two chronic and complex diseases whose prevalence in the older adult population is > 40% and 29%, respectively [1, 3]. Pharmacotherapy for both conditions is the fastest-growing therapy to treat older adults, and special considerations must be taken when treating older adults with GLP-1 RAs.

Despite the increasing use of GLP-1 RAs, there is still a lack of research on the effect of these medications on older adults. Older populations are frequently overlooked, and issues such as sarcopenia and functional decline must be considered [3, 4]. Clinically, it is important to understand older adults' goals for weight loss and glycemic control to ensure that what matters most to patients is always considered.

Aging is associated with progressive changes in body composition, including increased visceral fat and loss of skeletal muscle mass. These changes can create several problems in how our body uses energy, including an increased risk of insulin resistance and persistent high levels of inflammation. The development of obesity in older adults is closely linked to the development of multiple chronic diseases, such as T2DM,

cardiovascular disease, and metabolic syndrome. In some circumstances, there may be a common biological pathway between aging and obesity that could result in accelerated decline in physiological functions and possibly increased rates of morbidity and mortality. All these factors contribute to a significant clinical and public health impact of obesity and T2DM in older adults as a whole [5].

OVERVIEW OF GLUCAGON-LIKE PEPTIDE RECEPTOR AGONISTS

Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are two primary incretin hormones that are secreted by the intestine in response to glucose or nutrient ingestion. These hormones act via G protein-coupled receptors to enhance glucose-dependent insulin secretion from pancreatic β cells. In addition to their insulinotropic effects, GIP and GLP-1 play critical roles in various biological processes across multiple tissues and organs expressing GIPR and GLP-1R, including the pancreas, brain, cardiovascular and immune systems, gut, and kidney [6]. Glucagon secretion is inhibited by GLP-1, which also slows gastric emptying and stimulates central nervous system pathways that promote a feeling of fullness and reduce food intake. Similarly, GIP stimulates insulin secretion, improves lipid metabolism, and contributes to energy balance. Furthermore, the glucose-lowering and appetite-suppressing properties of GIP and GLP-1 provide the scientific basis for the current development of incretin-based treatments for T2DM and obesity [7].

Liraglutide

Liraglutide is a GLP-1 receptor agonist that was first approved in 2014 and is recommended for long-term weight management in adult patients with an initial body mass index (BMI) of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of at least one weight-related comorbid condition (hypertension, T2DM, or dyslipidemia). Its primary mechanisms, including appetite reduction, delayed gastric emptying, and enhanced insulin action, are particularly important in older adults who exhibit increased visceral fat and impaired metabolism due to sarcopenia and low-grade inflammation [8].

The SCALE (Satiety and Clinical Adiposity—Liraglutide Evidence) Obesity and Prediabetes Trial showed significant weight loss and improvements in glycated hemoglobin, fasting glucose, oral glucose tolerance test results, insulin resistance, and beta-cell function [9]. However, these studies predominantly included middle-aged participants, with limited representation of individuals aged ≥ 65 years and minimal inclusion of those ≥ 75 years [10]. Despite this limitation, pooled analyses suggested comparable average weight reduction between individuals younger and older than 65 years [11].

A reduction in cardiovascular risk has been demonstrated by liraglutide. In the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial, liraglutide reduced the risk of major adverse cardiovascular events (MACE), with a more pronounced effect observed in participants ≥ 75 years, showing a 34% reduction in risk. In the 60–74-year age group, liraglutide was associated with a 6% reduction in all-cause mortality compared with placebo. These findings support its role in older adults at high cardiovascular risk, although the limited representation of the oldest age groups remains a key limitation [12, 13].

Semaglutide

Semaglutide is a long-acting GLP-1 RA that has therapeutic effects through several connected physiological processes. It promotes insulin secretion, which depends on glucose, reduces inappropriate glucagon release, delays gastric emptying, and influences central pathways that regulate appetite. These actions lead to a long-term weight loss and improved glycemic control [14]. Its effects on inflammation, endothelial function, and atherosclerotic processes contribute to its cardiovascular and renal benefits [15, 16].

The clinical efficacy of semaglutide in obesity was demonstrated in a series of clinical trials, collectively termed the Semaglutide Treatment

Effect in People with Obesity Program (STEP 1–5). These trials showed substantial and sustained weight loss, which could be attributed to central appetite suppression, low caloric intake, and delayed gastric emptying [17].

In the STEP 1 Trial, participants without T2DM experienced an average weight reduction of 14.9% with semaglutide 2.4 mg compared with 2.4% with placebo, accompanied by improvements in physical functioning and cardiometabolic risk factors, including decreases in BMI, waist circumference, and blood pressure [18]. In the STEP 2 Trial, participants with obesity and T2DM achieved similar weight reductions of 9.6% versus 3.4% with placebo [19].

The role of central satiety pathways in mediating weight loss is further supported by the additive effect of behavioral therapy, as demonstrated in the STEP 3 Trial, with a 16% reduction in body weight being achieved by semaglutide [20]. Crucially, the STEP 4 Trial highlighted the necessity to continue the treatment for the benefits to last, as discontinuation led to significant weight gain. This underlines that obesity is a long-term condition, much like others, and often needs continuous care [21]. Long-term efficacy was confirmed in the STEP 5 trial; participants maintained an average weight loss of 15.2% for > 104 weeks. In addition to weight loss, the semaglutide group showed improvements in cardiometabolic parameters, such as blood pressure and lipid profiles [22].

Pooled analyses of the Semaglutide Unabated Sustainability in Treatment of T2DM (SUSTAIN Trials 1–5) phase 3 trials show a significant reduction in HbA1C levels, which are primarily explained by enhanced β-cell responsiveness and suppression of glucagon secretion in a glucose-dependent manner, minimizing the risk of hypoglycemia. These glycemic improvements were consistent in both younger (< 65 years) and older adults (≥ 65 years), alongside clinically meaningful weight loss [23]. These findings are further supported by a retrospective study from Spain involving older adults (mean age 76.5 years), which reported significant weight loss and improved glycemic control after 12 months of semaglutide therapy [24].

In addition to its metabolic effects, semaglutide has shown important cardiovascular benefits. In the SUSTAIN 6 and Peptide Innovation for Early Diabetes Treatment (PIONEER-6) trials, semaglutide reduced MACE by 24% [25, 26]. Meanwhile, the Semaglutide Effects on Cardiovascular Events in People with Overweight or Obesity (SELECT) trial showed a 20% reduction in cardiovascular events in participants with overweight or obesity without diabetes. These cardiovascular benefits are thought to be caused by several different processes, including anti-inflammatory effects, decreased oxidative stress, and regulation of lipid metabolism, along with weight reduction [14, 15].

Renal outcomes were assessed in the Evaluate Renal Function with Semaglutide Once Weekly trial (FLOW), in which semaglutide reduced major kidney disease events by 24%. Possible mechanisms for renal protection include improvements in glomerular hemodynamics, decreased systemic inflammation, and improved glycemic and blood pressure control [16]. Additional benefits were observed in patients with heart failure with a preserved ejection fraction; semaglutide improved both functional capacity and quality of life, as reported in the Semaglutide Treatment Effect in People with Obesity and Heart Failure with Preserved Ejection Fraction and Diabetes Mellitus trial (STEP-HFpEF DM) [27]. The mechanisms underlying these results may include reductions in systemic inflammation and adiposity, along with cardiometabolic effects associated with GLP-1 receptor activation [14].

Tirzepatide

Tirzepatide is the first dual GLP-1 and GIP receptor agonist approved for the treatment of obesity. The increased potency of tirzepatide relative to GLP-1 receptor agonists is thought to arise from complementary, possibly synergistic effects on metabolism. In addition to the actions of the GLP-1 RA, the GIP receptor agonist could enhance insulin release and influence adipose tissue metabolism and energy balance [7, 28].

In 2023, the US Food and Drug Administration approved tirzepatide for chronic weight management in adults with a BMI ≥ 30 kg/m^2 and those with a BMI ≥ 27 kg/m^2 with at least

one weight-related comorbidity. Clinical trials have demonstrated significant weight loss, with some participants achieving reductions of ≥ 20% of their body weight after 1 year of treatment [29].

The SURMOUNT-1 trial established the efficacy of tirzepatide in participants with obesity or overweight without diabetes, showing dose-dependent weight reductions of up to 20.9% at 72 weeks. Notably, a high proportion of participants achieved meaningful weight loss, with > 50% of those receiving higher doses (10 mg and 15 mg) achieving ≥ 20% body weight reduction. These outcomes reflect the potent combined incretin effect of dual receptor activation [30].

The SURMOUNT-2 trial demonstrated that improved glycemic control is accompanied by weight loss in participants with T2DM. This can be explained by tirzepatide's dual incretin signaling, which improves β-cell sensitivity and insulin release while reducing glucagon release [31]. Sustained receptor activation is necessary for long-term efficacy. The SURMOUNT-4 trial evaluated the maintenance of weight loss in participants with obesity and at least one weight-related comorbidity (such as hypertension, cardiovascular illness, obstructive sleep apnea [OSA], or hyperlipidemia) but without diabetes. Participants who received continuous tirzepatide experienced greater weight loss and maintained their prior weight loss, whereas those who discontinued tirzepatide experienced significant weight gain [32].

Pooled analysis of the SURPASS 1-5 trials demonstrated reductions in HbA1c levels and body weight in participants < 60 years compared with those aged ≥ 60, emphasizing the consistent metabolic benefits of tirzepatide. These improvements in glycemic control may be attributed to enhanced glucose-dependent insulin secretion and improved insulin sensitivity, which reduced the likelihood of hypoglycemia [33].

Tirzepatide has demonstrated cardiovascular and functional benefits. In participants with heart failure with preserved ejection fraction (HFpEF), tirzepatide reduced the incidence of heart failure episodes and improved patients' quality of life and physical exercise capacity. These effects may arise from adiposity reduction, anti-inflammatory activity, and cardiac workload reduction [34]. In addition, tirzepatide is effective against obesity-associated complications, such as obstructive sleep apnea (OSA), based on evidence obtained in the SURMOUNT-OSA trial. Significant reductions in the apnea-hypopnea index (AHI) were observed, an effect mainly attributed to weight loss [35].

Comparative Perspective and Clinical Implications

Incretin-based therapies consistently demonstrate benefits in glycemic control, weight reduction, and cardiovascular risk reduction. Among these medications, semaglutide and tirzepatide demonstrate more pronounced weight loss than liraglutide [1, 18, 30]. These differences may be attributed to their greater effects on appetite suppression and energy homeostasis. Tirzepatide also activates the glucose-dependent insulinotropic polypeptide (GIP) receptor, which may contribute to its effects [14].

However, we cannot be certain how these findings apply to older adults. Adults aged ≥ 75 years remain underrepresented in major clinical trials [5, 6]. This limits the ability to fully assess the efficacy and safety of these therapies in this population. This limitation is particularly relevant because aging is associated with increased frailty, sarcopenia, polypharmacy, and different responses to drugs. These factors may influence both the tolerance and clinical effectiveness of incretin-based therapies [7–9]. Therefore, dedicated studies in older populations are needed to better define optimal treatment strategies [5, 8]. For a closer look at clinical outcomes and evidence for older adults, refer to Table 1.

NUTRITIONAL CONSIDERATIONS IN OLDER ADULTS

Appropriate nutrition plays an important role in overall health and well-being. Inadequate nutrient intake, also known as malnutrition, is more prevalent among older adults. Chronic health conditions such as cancer, chronic obstructive

Table 1 Use of GLP-1 receptor agonist and tirzepatide in older adults: clinical outcomes

Medication	Mechanism	Population (age)	Evidence in older adult	Key outcomes	Weight reduction	Limitations
Liraglutide	GLP-1 RA	Mean ~45–46 years; limited ≥ 65	Limited (7% ≥ 65; 0.5% ≥ 75) [16]	Weight loss, reduction in HbA1c; reduced MACE [17]	~6–8.4 kg [14, 15]	Limited representation of oldest adults
Semaglutide	GLP-1 RA	Includes ≥ 65 subgroup	Moderate (pooled analyses ≥ 65) [25]	Strong weight loss, CV and renal risk reduction [3, 4]	~9.6–15.2% [20, 21, 24]	Increased gastrointestinal adverse events in older adults [24]
Tirzepatide	GIP + GLP-1	Mean ~45–65; subgroup ≥ 60	Emerging (≥ 60 subgroup data)	Greater weight loss, HFpEF, and OSA benefits [34, 35]	~15–21% [31, 32]	Limited data in ≥ 75 years

GLP-1 RA glucagon-like peptide-1 receptor agonist, *GIP* glucose-dependent insulinotropic peptides, *MACE* major adverse cardiovascular events, *CV* cardiovascular, *HFpEF* heart failure with preserved ejection fraction, *OSA* obstructive sleep apnea

pulmonary disease, and neurological conditions contribute to this increased risk, which explains why older are particularly vulnerable. Other considerations to examine in older adults include the presence or absence of dysphagia, the patient's hydration status, skin integrity, and bone health [36]. Malnutrition is associated with increased morbidity and mortality, as well as cognitive impairment, anemia, and longer hospital stays.

It is well established that older adults often experience reduced appetite and slower gastrointestinal transit, which contribute to malnutrition. Therefore, it is important to optimize dietary intake in older adults by providing energy-dense food options and prioritizing adequate protein intake [37].

SARCOPENIC OBESITY: IMPORTANCE IN OLDER ADULTS

Sarcopenic obesity (SO) is a global health problem, with a prevalence of approximately 11% in older adults, which increases with age. Studies report no significant sex differences in prevalence, implying that men and women are at equal risk [38]. SO refers to a clinical phenotype characterized by increased body fat (obesity) and decreased skeletal muscle mass and function (sarcopenia) [39]. The pathophysiology of SO involves several biological pathways, including age-related changes in body composition, hormonal changes, chronic inflammation, and chronic diseases such as insulin resistance [38, 40]. Notably, SO in older adults has significant health consequences, including disability, metabolic impairment such as dyslipidemia, increased overall mortality, and a detrimental impact on quality of life [40].

GLP-1 RAs, such as semaglutide, liraglutide, and tirzepatide, have emerged as novel treatment options for diabetes and obesity by improving insulin sensitivity and modulating inflammation, respectively [41]. Studies have shown that GLP-1 RAs can result in approximately 15–25% of weight loss. However, 25–40% of total weight loss may be lean mass in older adults [42]. It is well established that discontinuation of GLP-1 RAs is associated with weight regain, specifically through accumulation of a

greater proportion of adipose tissue. Additionally, weight cycling has been demonstrated to exacerbate sarcopenia by reducing lean mass and strength, particularly in individuals who have undergone more than six cycles of weight loss and regain [4].

Calorie restriction with adequate protein supplementation, resistance training, aerobic exercise, and smoking cessation remains a proven strategy for managing and preventing SO [4, 40, 43].

GLYCEMIC TARGETS AND TREATMENT GOALS IN OLDER ADULTS

Regular assessment of the medical, psychological, functional, and social domains is essential for the management of diabetes in older adults. Accurate assessment of diabetes type and duration, the presence of comorbidities, the patient's ability to self-manage their condition, the availability of social support, treatment burden, and treatment-related concerns, such as fear of hypoglycemia, polypharmacy, and financial barriers, is crucial when evaluating older adults with diabetes. Screening for diabetes-related complications in older adults should be personalized and frequently reviewed because these complications may influence treatment goals and therapeutic strategies [44].

According to the 2026 American Diabetes Association Standards of Care, glycemic targets for older adults should be individualized based on overall health status, comorbidities, cognitive function, functional status, and life expectancy. Healthy older adults with intact functional and cognitive status can aim for tighter glycemic control, targeting an A1C of about 7.0 to 7.5% and, when using continuous glucose monitoring, achieving a time in range of at least 70% (70 to 180 mg/dl). In contrast, older adults with intermediate or complex health status, including frailty or cognitive decline, should have less stringent glycemic goals, targeting an A1C of < 8.0% and a time in range of at least 50%. The main priority for these individuals should be safety and the avoidance of hypoglycemia. For older adults with very complex medical conditions or limited life expectancy, the focus should shift from strict glycemic targets toward preventing hypoglycemia and managing symptoms related to hyperglycemia [3].

BENEFITS OF USING GLUCAGON-LIKE PEPTIDE RECEPTOR AGONISTS IN OLDER ADULTS

GLP-1 RAs have demonstrated consistent metabolic, cardiovascular, and renal benefits in patients with T2DM and obesity. Across major clinical trials, GLP-1 RAs have been shown to significantly reduce the risk of MACE [14, 45–47], decrease the risk of renal failure and substantial declines in glomerular filtration rate, as reported in the LEADER study [16, 46], and improve glycemic control while promoting modest to substantial weight loss [10, 17, 18, 20–22].

In addition, GLP-1 RAs are associated with a low risk of hypoglycemia, representing a major advantage in frail older adults, as hypoglycemia is associated with an increased risk of falls and cognitive impairment [48]. Furthermore, GLP-1 RAs may allow for reductions in insulin and sulfonylurea doses when used in combination, thereby simplifying therapeutic regimens and reducing the risk of medication-related adverse effects [49].

SAFETY CONCERNS AND CONTRAINDICATIONS

The most frequently reported adverse effects (AEs) are gastrointestinal (GI), particularly in older adults, and when higher initial doses are prescribed, especially in those with dementia and existing comorbidities. GI symptoms, including nausea, vomiting, diarrhea, and

constipation, are generally mild, transient, and dose dependent. Their incidence may increase when GLP-1 RAs are used concomitantly with other medications, such as metformin, frequently leading to treatment discontinuation. Additionally, no correlation has been found between the use of long-acting formulations and an increase in GI symptoms [22, 23, 50]. Kiyosue et al. demonstrated that discontinuation of tirzepatide was higher among patients receiving doses of ≥ 10 mg, those with a BMI < 25 kg/m², and those aged ≥ 65 years [33].

GLP-1 RAs carry a boxed warning regarding thyroid C-cell tumors and pancreatitis. The risk of thyroid C cell tumors is based on findings in rodents; however, no increased risk has been demonstrated in humans beyond finding from animal studies and database analyses. Nevertheless, they are contraindicated if the patient has a history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 [50–52]. Some studies have reported the risk of suicidal thoughts and self-harm [52].

In addition, gallbladder-related events have been reported and appear to be associated with greater-than-average weight loss. Approximately half of pancreatitis cases were associated with gallstones [9, 22]. No significant cardiovascular adverse effects were reported, aside from an increase in resting heart rate [9].

Although the CV and renal benefits of using GLP-1 RAs are clinically significant, their use has been associated with an increase in renal adverse effects, particularly in patients with CKD and acute interstitial nephritis. Identified risk factors are advanced age, obesity, CKD, and the use of medications that may cause acute interstitial nephritis [53]. Age-related structural and functional changes in the kidney may contribute to this risk [54]. Overall, using GLP-1 RAs in patients with and without CKD appears to be safe, as current studies suggest these agents do not increase the overall risk of AKI, but they must be used with caution [52, 53].

POLYPHARMACY IN OLDER ADULTS

Older adults account for approximately 14% of the population in the US but use > 33% of prescription medications. Given this disproportionate medication utilization and chronic health conditions being more prevalent in this population, they are at an increased risk for polypharmacy. Polypharmacy is commonly defined as the routine use of five or more medications [55]. Studies have shown that among older adults, the overall prevalence is approximately 32% and increases with age [56].

Polypharmacy is an important concern in older adults due to its association with adverse drug effects, drug-drug interactions, medication nonadherence, an increased risk of hip fracture, and the potential for prescribing cascades. Age-related changes in pharmacokinetics, such as slower absorption, alterations in volume of distribution, and decreased elimination, should be considered in older adults [55]. In older adults, polypharmacy has been associated with clinical consequences such as frailty, increased risk of hospitalization, falls, increased mortality, and declining cognitive function [56]. Several strategies have been proposed to prevent polypharmacy in older adults, including medication reconciliation, reviewing medication changes with patients, prescribing the minimum necessary number of medications, discontinuing all unnecessary medications, and avoiding starting medications to treat potential side effects of other drugs [55].

T2DM is highly prevalent in older adults, making it a major contributor to polypharmacy [57]. GLP-1 RAs have been shown in many studies to be an effective therapy for diabetes mellitus and obesity, as well as an important agent for reducing polypharmacy in older adults with multiple chronic health conditions. This effect is attributed to their beneficial actions across multiple organ systems, such as cardiovascular, hepatic, neurological, and bone health [50]. In the current landscape, GLP-1 RAs have been proven to be a valuable option for the treatment of diabetes and obesity. Nevertheless, these agents (antiobesity medications) have been shown to affect the absorption of concomitant medications,

which should be considered during medication reconciliation before initiating a new anti-obesity medication [51]. Overall, polypharmacy remains a challenge in geriatric medicine.

OUTCOMES OF GLUCAGON-LIKE PEPTIDE RECEPTOR AGONISTS

Evidence from cardiovascular and renal outcome trials supports the efficacy of GLP-1 RAs in reducing the risk of renal disease progression and of renal- or cardiovascular-related mortality [14–16, 45–47].

Observational studies have suggested a possible association between GLP-1 RA use and a lower risk of dementia and cognitive decline in patients with type 2 diabetes [58–60]. However, evidence from randomized controlled trials remains limited. The EVOKE and EVOKE+ trials, which evaluated semaglutide in the early stages of Alzheimer's disease, did not demonstrate superiority over placebo in slowing disease progression, despite improvements observed in disease-related biomarkers [61–63]. Therefore, although preliminary findings are promising, additional research is needed to clarify the effects of GLP-1 RAs on cognitive outcomes.

Recent clinical trials have demonstrated improvements in metabolic and hepatic outcomes among patients with obesity and metabolically dysfunctional steatohepatitis treated with GLP-1 RAs [1]. In the SYNERGY-NASH trial, tirzepatide administered at doses of 5, 10, and 15 mg for 52 weeks resulted in higher rates of steatohepatitis resolution compared with placebo, along with improvements in liver enzyme levels, inflammatory biomarkers, and significant weight loss [64]. Similarly, the ESSENCE trial reported resolution of steatohepatitis and improvements in biochemical parameters after 72 weeks of semaglutide 2.4 mg once weekly [65]. Emerging evidence also suggests potential benefits in moderate-to-severe obstructive sleep apnea [35, 66].

GLP-1 RAs have been associated with reduced risk of certain obesity-related cancers, probably mediated by improvements in metabolic profile and systemic inflammation [1]. Semaglutide and liraglutide offer a broad therapeutic profile with established benefits in glycemic control, weight reduction, and cardiorenal outcomes, while potential neurological benefits remain under investigation.

Ethical and Quality-of-Life Considerations

The use of GLP-1 RAs in older adults requires a patient-focused approach and careful ethical consideration, prioritizing preservation of functional independence and quality of life instead of focusing exclusively on glycemic targets and weight reduction. Important factors identified for consideration regarding glycemic targets and treatment approaches include assessment of medical, psychological, and social determinants that may impact patient treatment and outcomes. Furthermore, screening for geriatric syndromes—such as polypharmacy, cognitive impairment, depression, urinary incontinence, and frailty—is also indispensable. Individualization of treatment must be a priority regarding life expectancy, frailty status, and comorbidities. Avoiding complex treatment plans is essential for decreasing the risk of hypoglycemia and polypharmacy. In addition, consider healthcare expenses and insurance coverage when creating treatment plans to minimize the risk of cost-related nonadherence [67].

Making collaborative decisions is fundamental, especially in older adults with cognitive impairment, comorbidities, or frailty, where the possible benefits of treatment must be balanced against AEs. The use of self-injecting and GI symptoms could be significant obstacles to adherence in older adults. In addition, appetite suppression, while favorable for weight loss, may be poorly tolerated in frail older adults, especially those at risk of malnutrition and sarcopenia [40]. Furthermore, GLP-1 RAs may predispose some older adults to inadequate nutritional intake, dehydration, and electrolyte imbalance. These risks accentuate the importance of hydration, adequate diet, and promotion of resistance training to preserve muscle mass, reduce nutritional imbalance, and prevent the progression of frailty [68].

Despite these obstacles, studies have shown the potential of GLP-1 RAs in treating obesity and its comorbidities in older adults. With meticulous consideration of patient eligibility,

adequate monitoring, and adjustment of treatment plans accordingly, GLP-1 RAs can lead to improvement in weight, glycemic control, and overall health effects [41].

FUTURE DIRECTIONS

Obesity continues to have a significant impact on healthcare. Older adults would benefit from specialized trials evaluating the outcomes of GLP-1 RAs in this population, particularly their effects on muscle mass and sarcopenia. Studies should emphasize not only the percentage of body weight loss but also changes in body composition during treatment. Future research should also focus on identifying specific subgroups most likely to benefit from this treatment and on establishing clinical guidelines to optimize its use. Additionally, strategies should be developed to reduce potential AEs and enhance treatment adherence [51].

From a healthcare perspective, the incorporation of continuous monitoring, therapy adjustments, and regular follow-up visits will help ensure that weight loss and glycemic control do not lead to unintended consequences.

CLINICAL PRACTICE RECOMMENDATIONS

The American Diabetes Association recommends prioritizing glucose-lowering therapies that minimize the risk of hypoglycemia, making GLP-1 receptor agonists an appropriate option for many older adults with T2DM [3]. GLP-1 RAs may have effects that extend beyond the treatment of diabetes and obesity. Emerging evidence suggest that GLP-1 RAs may help to improve health outcomes for patients with a variety of conditions, such as cardiovascular disease, obesity-related cancers, chronic kidney disease, and dementia [25, 69–72].

Data from large clinical studies support the significance of incretin-based therapies in metabolic management, including the SURMOUNT program, which evaluated tirzepatide, and the STEP program, which assessed semaglutide. These studies demonstrated significant reductions in body weight and glycated hemoglobin levels [17, 28]. However, physicians should carefully weigh the metabolic benefits against potential side effects such as gastrointestinal discomfort, dehydration, and excessive weight loss in older persons, especially those with frailty, sarcopenia risk, or low nutritional intake.

In clinical practice, it is usually recommended to start therapy at the lowest possible dose and gradually titrate the dose. To ensure that treatment benefits do not compromise nutritional status or physical independence, it is advised to regularly assess body weight, hydration status, muscle mass, and functional capacity. Periodic reassessment of therapeutic goals is essential to align treatment intensity with evolving patient priorities and health status [11].

CONCLUSION

GLP-1 RAs are key therapies for older adults with T2DM and obesity. Evidence from trials has demonstrated that GLP-1 RAs, such as semaglutide, liraglutide, and tirzepatide, are safe and effective therapeutic options that improve metabolic health.

In older adults, who usually experience polypharmacy, it is crucial to individualize treatment. Age-related structural and functional changes predispose these patients to a higher risk of sarcopenia and malnutrition. To avoid these outcomes, it is relevant to create and enhance strategies promoting resistance training and proper nutrition. Gastrointestinal adverse effects remain the most common treatment-related complications and may contribute to dehydration and nutritional decline status if not closely monitored. To ensure safety and tolerance, gradual titration and ongoing clinical follow-up are essential.

Overall, it should be a priority to preserve functional independence and quality of life rather than focus solely on glycemic levels and weight reduction. A patient-centered approach should guide decision-making, particularly for older adults with multiple comorbidities,

cognitive impairment, or frailty. Further studies are needed to evaluate changes in body composition during weight loss, characterize AEs, and their relationship to treatment discontinuation and dose dependency and to identify strategies to optimize treatment while balancing metabolic benefits with potential risks in this population.

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Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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