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Cardiovascular Safety of Testosterone Replacement Therapy in Hypogonadal Men

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Introduction

Testosterone replacement therapy (TRT) aims to restore serum testosterone levels in men with hypogonadism. Symptoms associated with hypogonadism include reduced libido, erectile dysfunction, fatigue, depression, and loss of muscle mass and bone density. The primary purpose of TRT is to alleviate these symptoms and improve quality of life by restoring serum testosterone levels to the physiological range.

The prevalence of hypogonadism in men increases with age, affecting approximately 2–5% of middle-aged and older men[1] and up to 20% of elderly men.[2] Despite its therapeutic benefits, the cardiovascular safety of TRT remains a topic of debate and investigation. Cardiovascular disease is a leading cause of morbidity and mortality among men, and any therapy that might influence cardiovascular risk requires careful evaluation. Early observational studies raised concerns about potential adverse cardiovascular outcomes associated with TRT. These findings prompted regulatory agencies to issue warnings and recommend further research. In response, more recent trials, including the TRAVERSE Study, have provided new insights into the relationship between TRT and cardiovascular health. This article aims to provide a review of recent evidence on the cardiovascular safety of TRT.

Physiological Role of Testosterone in Men

Testosterone influences numerous physiological processes, including muscle mass maintenance, bone density, libido, and mood regulation. Endogenously produced testosterone contributes to cardiovascular health by promoting vasodilation, modulating lipid profiles, and enhancing insulin sensitivity.[3]

Mechanisms of Testosterone's Influence on Cardiovascular Health

The mechanisms by which testosterone may influence cardiovascular health are complex and multifactorial. Testosterone is believed to exert both beneficial and potentially adverse effects on the cardiovascular system.

Vascular Function. The vasodilatory effects of testosterone contribute to its potential benefits in improving blood flow and reducing blood pressure. Testosterone stimulates the production of nitric oxide in endothelial cells, which in turn activates guanylate cyclase, increasing cyclic guanosine monophosphate levels, leading to muscle relaxation and vessel dilation. Testosterone can also modulate calcium channels in vascular smooth muscle cells, decreasing muscle contraction and promoting vasodilation by reducing intracellular calcium concentrations.[3]

Lipid Metabolism. Impact on lipid parameters in response to TRT has been mixed. Studies in hypogonadal healthy men, men with cardiovascular disease, metabolic syndrome and Type 2 diabetes (T2DM) show decrease in total cholesterol and low-density lipoprotein (LDL) by 5–14% from baseline with TRT. However, other studies have shown no effect. Similarly, HDL levels vary from increased to decreased to unchanged with TRT.[3] Proposed mechanisms for favourable changes in lipid profile include reduced *de novo* lipogenesis in adipose and liver tissue in response to testosterone. Testosterone also inhibits lipoprotein lipase activity and subsequent lower availability of free fatty acids in the bloodstream for uptake by tissues.[3]

Insulin Sensitivity. Hypogonadal men with T2DM and/or metabolic syndrome showed TRT- reduced homeostatic mechanism of insulin resistance by 15%.[4] This effect was confirmed using hyperinsulinemic euglycemic clamp studies, showing a 32% increase in glucose uptake after 6 months of TRT in men with T2DM and hypogonadotropic hypogonadism. The increase in insulin sensitivity was not related to change in lean mass, subcutaneous fat or visceral fat. However, expression of insulin signaling genes (IR-β, IRS-1, AKT-2, and GLUT4) was upregulated by more than 50% in adipose tissue after testosterone treatment compared with placebo.[5]

Conversely, testosterone can also stimulate erythropoiesis, potentially leading to increased blood viscosity and a higher risk of thromboembolic events. Graded doses of testosterone on erythropoiesis in healthy young and older men demonstrated that testosterone has a dose-dependent stimulatory effect on erythropoiesis. Both hemoglobin and hematocrit levels increased significantly in a linear fashion in response to testosterone doses, with older men showing a more pronounced response compared to younger men.[6]

Historical Perspective on TRT and Cardiovascular Risk

Initial observational studies and retrospective analyses suggested an association between TRT and increased cardiovascular events, such as myocardial infarction and stroke[7-9]. These findings led regulatory agencies like the FDA to mandate more rigorous safety labelling for testosterone products, emphasizing the potential risks.[10] These concerns led to a surge in research aimed at elucidating the true cardiovascular risks associated with TRT.

Recent large-scale trials studies, including the TRAVERSE study, have sought to address these concerns by providing more robust data on the cardiovascular outcomes of men undergoing TRT.

TRAVERSE Study

The TRAVERSE Study is one of the most extensive clinical trials to date investigating the cardiovascular safety of testosterone replacement therapy (TRT) in men with hypogonadism.[11]

Study Design and Population

This multicentre, randomized, double-blind, placebo-controlled trial included 5246 men aged 45 to 80 with symptomatic hypogonadism and either preexisting CV disease (CAD, CVD or PAD) or increased risk of CV disease (3 or more CV risk factors including hypertension, dyslipidemia, current smoking, stage 3 kidney disease, diabetes, elevated high sensitivity C-reactive protein, age 65 years or older, documented historical Agatston coronary calcium score greater than 75th percentile for age and race). Participants received either testosterone or a placebo gel, applied daily for a mean (±SD) duration of treatment of 21.7±14.1 months, and mean follow-up of 33.0±12.1 months). The primary endpoint was the occurrence of MACE, defined as a composite of myocardial infarction, stroke or cardiovascular-related death. Secondary endpoints included individual components of the

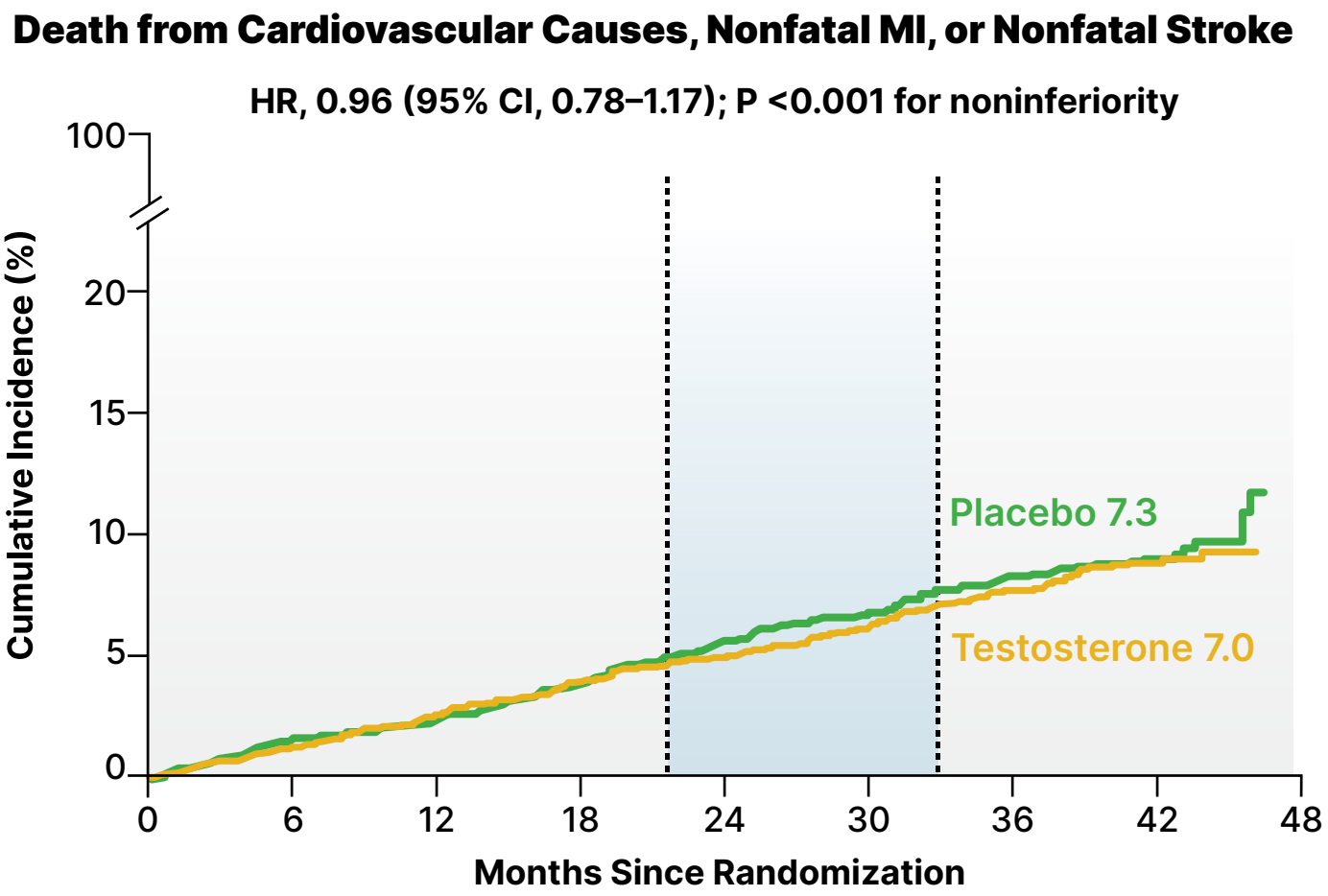

Figure 1. Incidence of major adverse cardiovascular events (MACE) in the TRAVERSE study; *adapted from Lincoff, AM, et al., 2023.*

primary endpoint, as well as other cardiovascular outcomes such as hospitalization for heart failure and coronary revascularization.

Results

The study found that the incidence of MACE was not significantly different between the testosterone and placebo groups. Specifically, 182 participants (7.0%) in the testosterone group experienced a MACE compared to 190 participants (7.3%) in the placebo group (HR 0.96; 95% CI, 0.78 to 1.17). The incidence rates of the primary endpoint were similar between the testosterone and placebo groups, suggesting that TRT does not exacerbate the risk of major cardiovascular events in this high-risk population. These results are pivotal, as they provide reassurance about the cardiovascular safety of TRT when administered under controlled conditions to appropriately selected men.

Adverse Events

While the TRAVERSE Study largely supports the cardiovascular safety of TRT, it also evaluated several adverse events associated with testosterone therapy. The study reported increased prostate-specific antigen (PSA) levels in the TRT group (P <0.001). Non-fatal arrhythmias warranting intervention, as well as atrial fibrillation, were significantly higher in the TRT group (5.2% vs. 3.3%, 3.5% vs. 2.4% respectively). Acute kidney injury occurred in 2.3% of the TRT group and 1.5% of the placebo group. The incidence of pulmonary embolism was also higher with testosterone than with placebo (0.9% vs. 0.5%, respectively).[11]

In addition to cardiovascular outcomes, the TRAVERSE Study examined bone health and fracture risk among participants. Bone density measurements indicated that TRT was associated with increased bone mineral density (BMD) at the lumbar spine and hip, suggesting potential benefits for skeletal health. However, despite these improvements in BMD, there

was an unexpected increase in the incidence of fractures in the TRT group compared to the placebo group. The fracture rate was 3.5% in the TRT group vs. 2.46% in the placebo group (HR 1.43, 95% CI, 1.04 to 1.97). Most fractures in both groups were associated with trauma, more commonly with falls, most commonly affecting the ribs, wrist and ankle[12]. This finding indicates a potential area of concern and suggests that while cardiovascular risks may not be heightened, other risks such as bone health require further investigation and careful management in clinical practice.

Testosterone Trials (TTrials)[13]

The Testosterone Trials consist of a series of seven coordinated trials aimed at determining the efficacy and safety of TRT in older men with low testosterone levels. These trials encompass various health aspects, including sexual function, physical function, vitality, cognitive function, bone density, anemia, and cardiovascular health. The Cardiovascular Trial within the TTrials specifically assessed the impact of TRT on coronary artery plaque volume (**Table 1**).

The cardiovascular trial involved 170 men aged 65 and older who were randomly assigned to receive either testosterone gel or a placebo for one year. The primary outcome measured was the change in coronary artery plaque volume, assessed through coronary computed tomography angiography. No participants in the treatment or placebo group were reported to have a major adverse cardiovascular event.

The results indicated a significant increase in non-calcified plaque volume in men receiving TRT compared to those receiving placebo. However, these findings were not associated with an increased incidence of cardiovascular events during the study period, warranting further investigation into the long-term implications.

T4DM Trial[14]

The Testosterone for Diabetes Mellitus (T4DM) trial was a randomized, double-blind, placebo-controlled trial. The primary objective was to evaluate whether or not testosterone therapy combined with lifestyle intervention could reduce the incidence of T2DM in men at high risk. The study included 1007 men aged 50–74 years with a waist circumference of >95 cm who had impaired glucose tolerance or newly diagnosed T2DM had low testosterone levels.

The participants were randomly assigned to receive either testosterone therapy or a placebo, alongside a structured lifestyle program. Over the two-year study period, the results demonstrated that the group receiving testosterone therapy had a significantly reduced risk of developing T2DM compared to the placebo group. There was no significant difference in the incidence of cardiovascular events between the TRT and the placebo group. This finding suggests that testosterone therapy did not increase the risk of cardiovascular events over the two-year study period. Additionally, the testosterone group experienced significant improvements in body composition, insulin sensitivity, and glycemic control, which are beneficial factors for cardiovascular health.

TEAAM Trial[15]

The Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) trial investigated the impact of TRT on atherosclerosis progression in older men. This double-blind, placebo-controlled trial enrolled 308 men aged 60 years or older with low or low-normal testosterone levels and followed them for three years. Co-primary outcomes included carotid artery intima-media thickness and coronary artery calcium score.

The study found no significant difference between the TRT and placebo groups, suggesting that TRT does not accelerate atherosclerosis progression in older men.

Discussion

The cardiovascular safety of TRT has been a contentious issue, with early studies suggesting increased risks and more recent trials providing reassuring evidence. While recent trials have provided valuable insights into the cardiovascular safety of TRT, several areas warrant further research. Long-term studies are needed to assess the impact of TRT on cardiovascular outcomes in diverse populations, including men with varying degrees of cardiovascular risk.

The TRAVERSE Study revealed several unexpected adverse events in the testosterone treatment group, including an increased incidence of fractures, atrial fibrillation, and nonfatal arrhythmias. These findings raise concerns about the comprehensive safety profile of TRT and underscore the need for further investigation. While TRT has demonstrated benefits in symptom

Study Name	Study Design and Methods	Age of Study Population	Baseline Testosterone Levels (*nmol/L*)	Testosterone Administered	Study Duration	Cardiovascular Outcomes	Adverse Events
TRAVERSE Study	Randomized, double-blind, placebo-controlled	45-80 years	≤10.4	1% testosterone gel daily	3 years	No significant difference in incidence of MACE between testosterone and placebo groups (HR 0.96; 95% CI, 0.78–1.17)	Increased PSA. Increased incidence of arrhythmia, atrial fibrillation, pulmonary embolism, fractures, and acute kidney injury
Cardiovascular T Trial	Randomized, double-blind, placebo-controlled	≥65 years	≤9.5	Testosterone gel	1 year	Increased non-calcified coronary artery plaque volume in testosterone group (P=0.003); no difference in MACE	Increased hemoglobin and hematocrit levels in the testosterone group
TEAAM Trial	Randomized, double-blind, placebo-controlled	≥60 years	3.46–13.9	Testosterone gel	3 years	No significant effect on progression of subclinical atherosclerosis measured by carotid artery intima-media thickness (CIMT) and coronary artery calcium (CAC)	Increased erythrocytosis and PSA in testosterone group
T4DM Trial	Randomized, double-blind, placebo-controlled	50–74 years	≤14.0	1000 mg testosterone undecanoate every 3 months	2 years	Reduced incidence of T2D (RR 0.59; 95% CI, 0.43–0.80). No significant increase in MACE.	Increased risk of erythrocytosis

Table 1. Summary of key cardiovascular trials on testosterone replacement therapy; *courtesy of Jagoda Kissock, MD, FRCPC.*

relief and metabolic health improvements, the emergence of these adverse events suggests a more complex risk-benefit landscape that must be thoroughly evaluated.

Future research should focus on identifying the patient populations at highest risk for these adverse events and elucidating the underlying pathophysiological mechanisms. Longitudinal studies with larger sample sizes and extended follow-up periods are necessary to assess the long-term cardiovascular and skeletal impacts of TRT. Additionally, examining the role of various testosterone formulations and dosing regimens in modulating these risks could provide valuable insights for optimizing treatment regimens.

Conclusion

The cardiovascular safety of TRT in men remains a critical concern for clinicians. Recent studies, including the TRAVERSE study, provide reassuring evidence that TRT does not significantly increase the risk of cardiovascular events in men with hypogonadism. However, careful patient selection, monitoring and individualized treatment approaches are essential to minimize potential risks and maximize benefits. Continued research is needed to further elucidate the long-term cardiovascular effects of TRT and guide clinical practice.

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Financial Disclosures

Advisory Boards: Abbott, NovoNordisk

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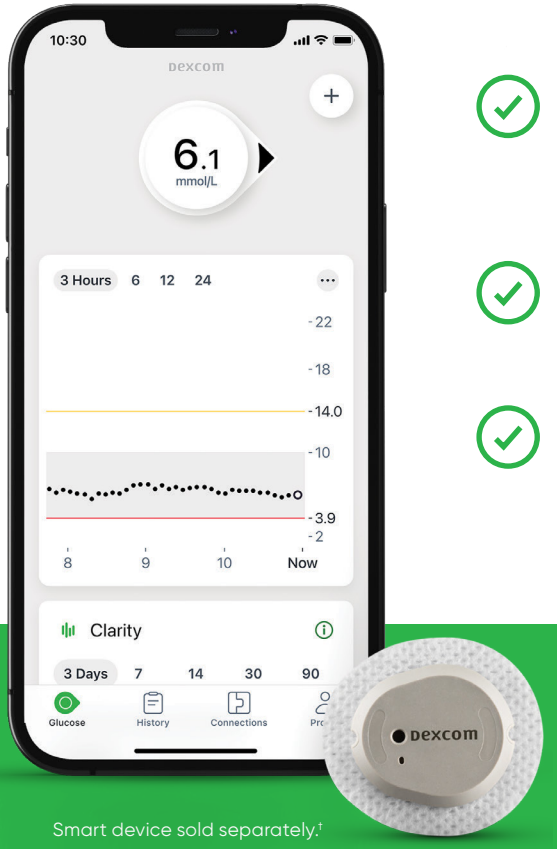

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§ Based on data from Dexcom CGM users in the U.S.

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The Role of Bisphosphonate Drug Holidays in the Management of Osteoporosis

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Introduction

Osteoporosis is a chronic skeletal disorder of compromised bone strength leading to an increased risk of fragility fractures, particularly with advancing age.[1] More than 2 million Canadians are living with osteoporosis,[2] and osteoporotic fractures are associated with considerable morbidity, increased mortality, and high economic burden to the healthcare system.[3] The ultimate goal of osteoporosis pharmacotherapy is to reduce the risk of fragility fractures.

Bisphosphonates are the most widely used first-line medications for osteoporosis due to their robust anti-fracture efficacy and favourable safety profile,[4] as demonstrated in short-term randomized placebo-controlled trials of 3-years duration with fracture outcome assessed as the primary endpoint.[5] However, the optimal duration of bisphosphonate therapy has been questioned regarding their long-term efficacy and safety given their long half-life in bone.[6] Prolonged use is associated with very rare but serious adverse complications such as atypical femoral fracture (AFF) and osteonecrosis of the jaw (ONJ).[7,8] Moreover, while extension trials indicate that long-term bisphosphonate therapy helps maintain bone density, the evidence supporting further fracture risk reduction with prolonged treatment is less convincing.[9-11] Regarding concerns about rare adverse effects and the attenuated benefit-to-risk ratio with long-term use, several professional organizations have issued guidelines suggesting bisphosphonate drug holidays.[4,11] This approach aims to minimize prolonged exposure and mitigate rare risks while preserving some residual anti-fracture benefits from the persistent drug in the skeleton.[4,11] Here, we review the role of bisphosphonate drug holidays in the long-term management of osteoporosis, the supporting evidence, recommended guidelines on treatment duration, along with key considerations for implementing a bisphosphonate drug holiday.

What Is a Drug Holiday and How Does It Apply to Bisphosphonates?

A drug holiday is defined as the deliberate interruption of pharmacotherapy for a defined period and for a specific clinical purpose.[12] Drug holidays are rarely recommended for chronic conditions since interruption of medical therapy can be harmful in such cases. However, bisphosphonates are unique in the management of osteoporosis. Although their half-lives in the plasma are short, after a baseline period of exposure, bisphosphonates have extended effects on the skeleton as they bind avidly with hydroxyapatite crystals of bone surfaces and become part of the bone matrix.[13] Consequently, bisphosphonates can remain stored in the bone for many years after stopping treatment, continuing to suppress osteoclast-mediated bone resorption. They are gradually released from the bone and reused, leading to a lasting though gradually diminishing anti-resorptive effect.[6,13] This distinct characteristic of bisphosphonates not only raises concerns about the potential risks of extended "over-suppression" of bone turnover, which can hinder bone remodelling essential for repairing skeletal microdamage, but also underscores their clinical effectiveness during a bisphosphonate drug holiday.

Differences in Bisphosphonates

Alendronate, risedronate, and zoledronic acid are potent nitrogen-containing bisphosphonates recommended as first-line pharmacotherapy for osteoporosis in Canada.[4] Oral bisphosphonates have been more widely used due to their ease of accessibility and low cost, whereas intravenous zoledronic acid has been typically used in settings of gastrointestinal intolerance or contraindications to oral bisphosphonates. While comparative head-to-head trials are lacking, a network meta-analysis suggests that the differences in effectiveness among these bisphosphonates in reducing the risk of vertebral, nonvertebral, and hip fractures are likely overall small.[5] However, these bisphosphonates differ in their pharmacokinetic properties in terms of their anti-resorptive potency on osteoclasts, as well as their binding affinity to bone, which may modify their duration of effects during a drug holiday.[6,13] Zoledronic acid has the highest binding affinity, followed by alendronate, then by risedronate.[6] As a result, the anti-fracture benefits may diminish more quickly after discontinuing risedronate compared to alendronate, while zoledronic acid is anticipated to have the longest lasting effects once treatment is stopped.

Evidence From Withdrawal Extension Trials

In line with the pharmacologic properties of bisphosphonates, evidence from 2 randomized withdrawal extension trials[9,10] evaluating the effects of continuing versus discontinuing bisphosphonate treatment, suggest that fracture risk reduction can be maintained for years after

stopping bisphosphonate treatment. These findings support the concept and safety of bisphosphonate drug holidays.

The Fracture Intervention Long-term Extension (FLEX) trial[9] randomized a subset of participants from the original Fracture Intervention Trial (FIT).[14,15] These participants had already received 3–4 years of alendronate and up to 1 year of open-label alendronate. They were assigned to either continue alendronate for 10 years or to discontinue alendronate for a drug holiday for the next 5 years. Comparing 10 years of continued alendronate versus an average of 5 years of alendronate followed by a drug holiday of 5 years, there was a gradual decline in bone mineral density (BMD) and a rise in bone turnover markers (BTMs) in the drug holiday group, though the BMD and BTMs did not return to their pretreatment levels.[9] Fracture risk reduction was an exploratory endpoint and there was no difference in all clinical, nonvertebral, or morphometric vertebral fractures in those who stopped alendronate after 5 years compared to those who continued therapy for 10 years.[9] However, there was a statistically significant lower rate of clinical vertebral fractures in the extended alendronate group (2.4%) versus those in the drug holiday group (5.3%). Subgroup analysis suggests that the greatest reductions in clinical vertebral fractures with extended alendronate occur in women with a T-score of ≤-2.5 at the femoral neck at FLEX baseline and in those with a baseline vertebral fracture.[9]

Similarly, the HORIZON extension trial[10] randomized a subset of participants from the original HORIZON-Pivotal Fracture Trial.[16] These participants had already received 3 annual intravenous (IV) infusions of zoledronic acid and were then assigned to either continue yearly zoledronic acid for an additional 3 years versus stop treatment for a drug holiday. A drug holiday of 3 years after annual zoledronic acid treatment for 3 years resulted in a mild decline in BMD and a slight rise in BTMs compared to ongoing therapy for 6 years. However, the BMD and BTMs were still better compared to pretreatment values. Fractures assessed as secondary endpoints showed no difference in all clinical, clinical vertebral, nonvertebral, or hip fractures in those who stopped zoledronic acid for a drug holiday after 3 years of therapy compared to those who continued therapy for 6 years. However, there were fewer new morphometric vertebral fractures in the extended treatment group (odds ratio = 0.51; p=0.035)[10]. A post-hoc subgroup analysis suggests that this benefit in reducing morphometric vertebral fractures with extended therapy is greatest in those with a total hip or femoral neck T-score of ≤-2.5 and in those with an incident morphometric vertebral fracture during the initial 3 years of zoledronic acid therapy.[17] A second extension of the HORIZON trial,[18] examining annual zoledronic acid for 9 years, versus annual zoledronic acid for 6 years followed by a drug holiday of 3-years, showed no differences in the rate of bone loss and no differences in fractures between the 2 groups.

In summary, evidence from withdrawal extension trials of alendronate and zoledronic acid suggest residual anti-fracture benefits for up to 3–5 years after stopping bisphosphonate treatment. Continuation of therapy does not appear to provide further benefit of reducing all clinical and nonvertebral fractures and may inconsistently reduce vertebral fractures. The reported mixed reduction of vertebral fractures should be interpreted with caution, especially considering that one trial showed a decrease in clinical vertebral fractures, but not morphometric vertebral fractures, while the other trial reported the opposite. Furthermore, it is important to note that a limitation of these extension trials is that bone density changes were the primary endpoint, while fractures were exploratory endpoints owing to small sample sizes.

Although the extension of the Vertebral Efficacy with Risedronate Therapy (VERT-NA) study showed that the risk of new morphometric vertebral fracture remains reduced 1 year after stopping risedronate following 3 years of treatment, despite decreases in BMD and a rise in BTMs,[19] there is no comparable withdrawal extension trial for risedronate.

Evidence from Real-World Studies

Real-world studies offer additional insight into the relative safety of bisphosphonate drug holidays observed in everyday clinical practice. A recent large systematic review that examined real-world studies evaluating bisphosphonate drug holidays found that even after adjusting for various clinical factors that may influence decisions regarding drug holidays, discontinuing bisphosphonate therapy after at least 3 years of treatment was generally safe with no significant rise in fractures during a monitoring period of up to 5 years.[20] These studies primarily included postmenopausal women, with a mean age of 69–75 years, and adherence rates

Years of Bisphosphonate Use	Incidence Rate per 10,000 person-yr
<0.25	0.1 (AFF=4)
0.25 to <3	0.6 (AFF=35)
3 to <5	2.5 (AFF=50)
5 to <8	6.0 (AFF=93)
≥8	13.1 (AFF=95)

Table 1. AFFs according to cumulative bisphosphonate exposure; *adapted from Black, DM, et al., 2020.*

Abbreviations: AFF: atypical femoral fracture

to oral or intravenous bisphosphonate treatments ranged from >50% to 80%. High adherence was recognized as a key factor in maintaining reduced fracture risk during a bisphosphonate drug holiday; while poor adherence, lower baseline BMD, previous fractures, and age >78 years were identified as risk factors for drug-holiday related fractures in the real-world studies.[20] Changes in BMD and BTM were more notable in those who stopped oral bisphosphonates versus IV bisphosphonates during drug holidays, with a suggested trend toward increased fractures in oral bisphosphonate users, particularly with risedronate.[20]

Impact on Rare Adverse Effects

While randomized controlled trials do not provide sufficient data about rare harms related to long-term bisphosphonate treatment, real-world observational studies clearly demonstrate the duration-dependent association between bisphosphonate use and AFF. A large prospective cohort study[7] indicates that although the absolute risk of AFF is very low compared to the higher number of osteoporotic fractures that are prevented by bisphosphonates, the frequency of AFF significantly increases with longer bisphosphonate use. The incidence rises from 2.5 AFFs per 10,000 person-years with 3–5 years of treatment, to 13.1 per 10,000 person-years after more than 8 years of exposure (**Table 1**). The risk of AFF was 5 times higher in Asian women compared to Caucasian women. However, the risk of AFF declines rapidly upon bisphosphonate discontinuation. Even a 1-year drug holiday leads to a significant reduction of AFFs, with the risk nearly returning to baseline levels of 0.6 per 10,000 person-years after 15–48 months off medication, despite the drug's long-term presence in the bone (**Table 2**). These data suggest that although the benefits of bisphosphonates outweigh the rare risk of AFF in the early stages of treatment, the balance becomes less certain for long-term users, particularly among Asian women. It also underscores the beneficial effect of a bisphosphonate drug holiday, even as short as 1 year, in reducing the risk of AFF.

ONJ is more commonly linked to higher-dose bisphosphonate regimens used in cancer treatment. However, the incidence is much lower with bisphosphonate dosing for osteoporosis, with an estimated risk of 2.5 cases per 10,000 patient-years.[8,21] While there seems to be a trend suggesting an increased risk of ONJ with longer cumulative bisphosphonate use, roughly doubling after more than 5-years of exposure,[8] the evidence supporting this is of low quality.[22] Additionally, no studies have yet examined the incidence of ONJ in patients at various points after discontinuing bisphosphonates for a drug holiday.

Suggested Approach to Bisphosphonate Drug Holidays

Several organizations have proposed approaches to bisphosphonate drug holidays in the long-term management of osteoporosis.[4,11] In light of limited evidence, it is unsurprising that guidelines vary on who should take bisphosphonate drug holidays, when they should be initiated, how long they should last, and the criteria for restarting

Months Since Discontinuation of Bisphosphonate	Incidence Rate per 10,000 person-yr
Not yet used	0 (AFF=1)
≤3	4.5 (AFF=200)
>3 to 15	1.8 (AFF=46)
>15 to 48	0.6 (AFF=18)
>48	0.5 (AFF=12)

Table 2. AFFs according to time since bisphosphonate discontinuation; *adapted from Black, DM, et al., 2020.*

Abbreviations: AFF: atypical femoral fracture

therapy. However, most guidelines emphasize the importance of individualizing the approach from a benefit-risk perspective, clinical factors, and patient preference.

The 2023 Osteoporosis Canada Clinical Practice Guideline[4] recommended considering bisphosphonate discontinuation for a drug holiday in all individuals after an initial treatment duration of 3–6 years (**Figure 1**). Individuals at higher risk for fractures, such as those with prior hip, vertebral, or multiple fractures, or those with new or ongoing active risk factors for accelerated bone or fractures should be treated for at least 6 years.

Suitable candidates for a bisphosphonate drug holiday include those who have adhered well to treatment and have shown a good response to the initial bisphosphonate course (e.g., stable/improved bone density and no fractures during treatment). It is suggested that after 3 years off bisphosphonate therapy, patients should be reevaluated for resuming treatment, based on updated BMD and clinical assessment of fracture risk (**Figure 1**). Treatment should be restarted for those who continue to meet the treatment threshold outlined in the guidelines.[4] However, an earlier reassessment than 3 years to resume treatment may be appropriate in those with a higher risk of fracture (such as prior hip or vertebral fracture, or a high Fracture Risk Assessment Tool [FRAX] score), secondary causes of osteoporosis, new fracture, or those with new clinical risk factors associated with rapid bone loss (**Table 3**). The decision to restart therapy sooner for a shorter drug holiday may also be influenced by the overall bisphosphonate exposure (e.g., shorter treatment duration or suboptimal adherence) and the specific bisphosphonate used, with risedronate having the shortest-lived protective effect in bone during a drug holiday (**Table 3**).[4,11] Current evidence does not support the use of BTMs in decisions about bisphosphonate drug holidays.[4,11,20]

A bisphosphonate drug holiday is not recommended if there are concerns about inadequate treatment response or ongoing substantial concern for fracture during the initial treatment period (**Figure 1**).[4] Inadequate response can be defined by the occurrence of new fractures or significant bone density decline (e.g., ≥5%) despite adherence to an appropriate course of bisphosphonate therapy.[4] Adherence to bisphosphonate therapy is consistently low in published studies[23,24] and should be ruled out when there are concerns about inadequate response. Substantial concerns for fracture may involve individuals with active risk factors such as steroid use, other secondary causes, or comorbidities linked to a high fracture risk, particularly in the very elderly.

If a bisphosphonate drug holiday is deemed inappropriate and not recommended, continuing bisphosphonate therapy or switching to an alternative medication is advised as the benefits of continued therapy likely outweigh potential rare harms in these patients (**Figure 1**).[4] Nonetheless, the decision to extend bisphosphonate treatment versus switching to a different class of medication should consider a patient's individualized risk for AFF and ONJ (**Table 4**). Continuing bisphosphonate therapy, including transitioning to IV bisphosphonate, may be a suitable option for individuals with a history of poor

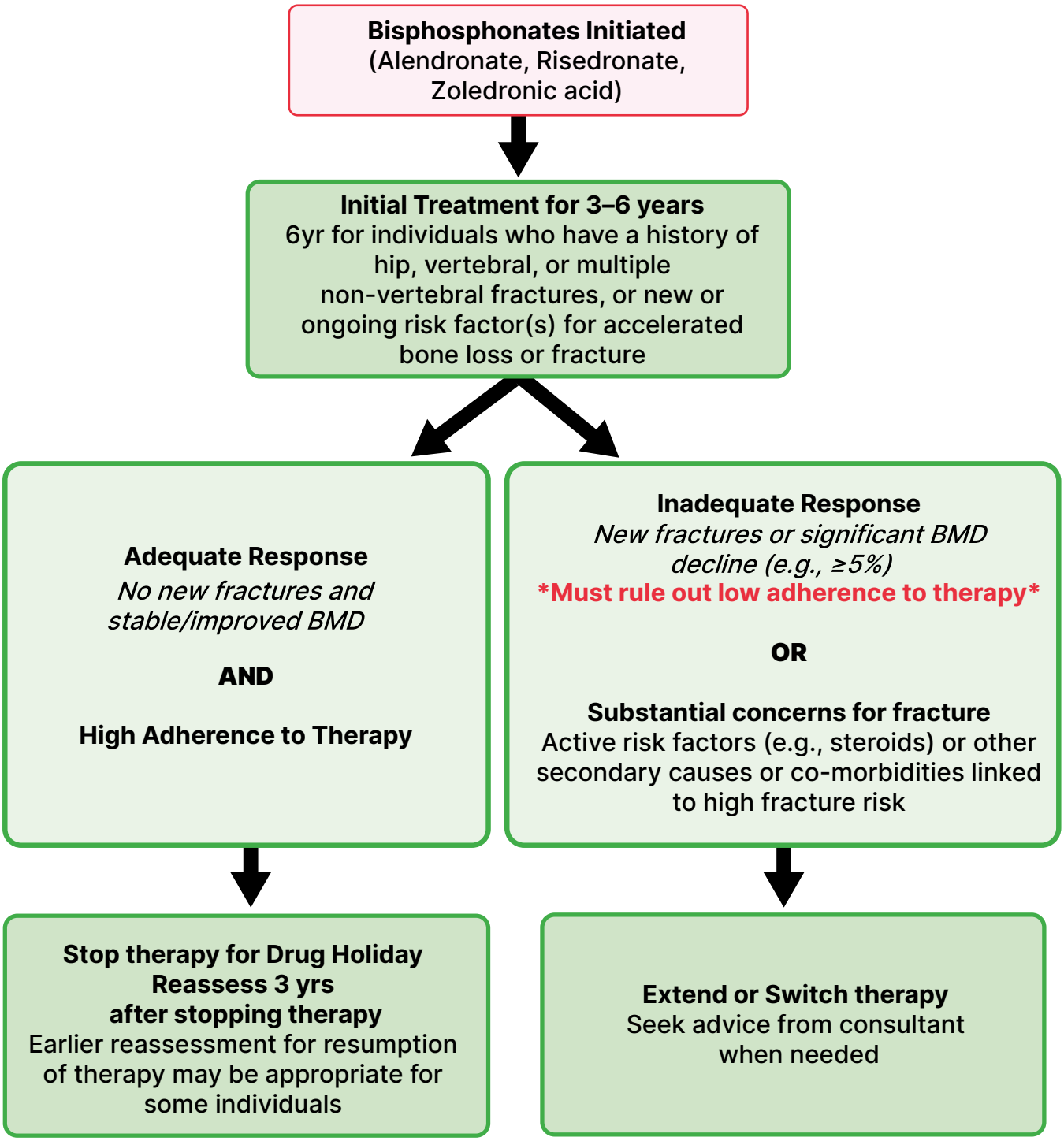

Figure 1. Suggested approach to bisphosphonate duration and drug holiday; *adapted from Morin, SN, et al., 2023.*

Abbreviations: BMD: bone mineral density

Factors that May Warrant a Shorter Bisphosphonate Drug Holiday[4,11]
• Prior hip or vertebral fracture(s)
• Very high fracture risk (e.g., high Fracture Risk Assessment Tool [FRAX] score with low bone mineral density [BMD] and older age considered)
• New fracture(s)
• New clinical risk factor(s) or active secondary cause(s) for osteoporosis or fracture (e.g. glucocorticoid use, aromatase-inhibitor therapy, androgen-deprivation therapy, falls)
• Shorter treatment duration or suboptimal adherence
• Use of risedronate (versus alendronate or zoledronic acid)

Table 3. Factors that may warrant a shorter bisphosphonate drug holiday.

Risk Factors for Rare Adverse Effects with Bisphosphonate Therapy[4,7,8,21]	
Atypical Femoral Fracture (AFF)	**Osteonecrosis of the Jaw (ONJ)**
Longer bisphosphonate duration> 5–8 years	Long-term bisphosphonate use >5 years
Asian ethnicity	Higher bisphosphonate dosing used in cancer
Shorter height, higher weight	Poor dental health, invasive dental surgery
Glucocorticoid use	Glucocorticoid use

Table 4. Key risk factors for bisphosphonate-related AFF and ONJ.

treatment adherence. For individuals at a higher risk of developing AFF or ONJ, switching to an anabolic agent may be a better option. Denosumab is also linked to the risk of AFF and ONJ.[4] Additionally, the challenges of implementing a drug holiday with denosumab, due to the risk of rapid bone loss and rebound vertebral fractures after discontinuation, should be taken into account when considering this treatment option.[4]

Conclusion

Osteoporosis is a chronic progressive disorder that requires long-term management. However, extended bisphosphonate therapy is linked to rare adverse effects, and, after a certain duration, further significant anti-fracture benefits are unlikely. Bisphosphonate drug holidays take advantage of the drug's unique durability in bone beyond their period of use. Extension trials and real-world studies demonstrate that in the vast majority of patients, a bisphosphonate drug holiday can be safely implemented after adherent therapy for 3–6 years, and the risk of AFF rapidly declines even after a 1-year drug holiday. However, the residual anti-fracture effects diminish over time, therefore; careful planning of treatment resumption is needed, particularly in those who remain at higher risk for fractures. Guidelines suggest an approach to bisphosphonate drug holidays but emphasize a tailored approach from a benefit-risk perspective, weighing clinical risk factors for both osteoporotic fractures and rare adverse effects. Further research on intermittent bisphosphonate treatment and sequential therapy may help identify improved long-term strategies for reducing fracture risk and minimizing harm.

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Financial Disclosures

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A.L.: None declared.

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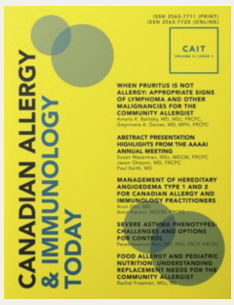

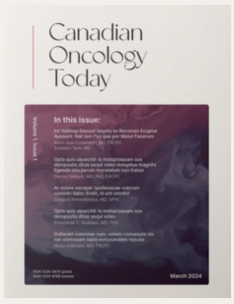

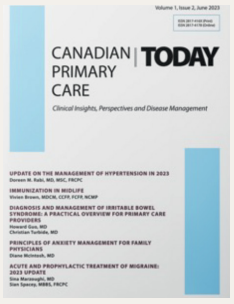

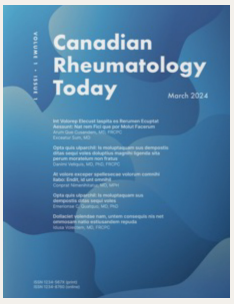

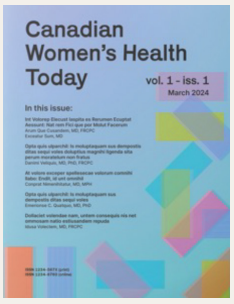

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Treatment of Obesity in Individuals with Type 1 Diabetes

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The prevalence of obesity (OB) is increasing among individuals with type 1 diabetes (T1D), posing unique challenges for managing their blood sugar levels and long-term health. Unlike type 2 diabetes (T2D), which is closely linked to OB and insulin resistance (IR), addressing OB in T1D requires careful consideration, because patients rely on external insulin, which can contribute to weight gain. In this review, we will discuss the causes and complications of OB in individuals with T1D, current approaches to treatment, potential lifestyle, and medical, and surgical interventions to manage weight while effectively maintaining optimal blood sugar control.

Introduction

In the past, type 1 diabetes (T1D) was commonly associated with a lean body type. However, in recent years, there has been a significant increase in the prevalence of overweight (OW) and obesity (OB) among individuals with T1D, with rates approaching those of the general population.[1,2] For instance, a study in the USA found that 34% of adults with T1D were OW, and 28% were affected by OB.[3] In Canada, one registry reported that 34.6% of adults with T1D were OW, and 19.8% were affected by OB.[4] Similar trends have been observed in studies from other parts of the world.[5-8]

Research has shown that a significant number of children and adolescents with T1D also struggle with OW and OB. According to the SEARCH for Diabetes in Youth study, 22.1% of children and adolescents with T1D in the USA (aged 3–19 years) were OW, compared to 16.1% of their peers without T1D. Additionally, 12.6% of them were affected by OB, compared to 16.9% of their peers without T1D.[9] Another study of 5529 adolescents (aged 13–18 years) in the T1D Exchange registry in the USA found similar or slightly higher rates of OW (22.9%) and OB (13.1%).[10] Globally, data from the international SWEET registry, which included 55 pediatric diabetes centres and over 30,000 individuals from all continents, reported that the prevalence of OW and OB among children and adolescents with T1D (aged 2–18 years) was 27.2% for girls and 22.3% for boys.[11]

This evolving situation brings added challenges to T1D management, as OW and OB can worsen insulin resistance (IR) and raise the risk of heart disease, hypertension, and dyslipidemia. Addressing OB in T1D requires special attention to how insulin treatment affects weight gain and blood sugar control.

It is becoming more evident that insulin use in individuals living with T1D can impact body composition and lead to an excess accumulation of fat, posing health risks. Additionally, there is a rising concern that T1D is more likely to occur in individuals with OW and OB. The accelerator hypothesis suggests that the line between T1D and T2D is becoming less

clear, as weight gain is consistently identified as a significant factor for both conditions.[12,13]

This review delves into the unique challenges and strategies for treating OB in individuals with T1D, focusing on the pathophysiology and complications of OB. It also covers a range of interventions, from lifestyle changes to pharmacologic approaches and metabolic surgery, as well as the emerging role of new weight management medications. These strategies are crucial in addressing the complex interplay between OB and T1D.

Pathophysiology of Obesity in T1D

Despite the apparent paradox, OB in individuals with T1D is a complex outcome of multiple factors:

- ***Genetic predisposition:*** Some data suggest that genetic factors play a role in the development of OB in individuals with T1D. A study on a cohort of 1119 children with T1D revealed an association between body mass index (BMI) and known OB susceptibility genes.[14] Fat mass and the OB-associated (*FTO*) gene is associated with higher BMI in individuals with T1D.[14] In the Diabetes Control and Complications Trial (DCCT), it was demonstrated that individuals with T1D on intensive insulin therapy with a family history of T2D gained more weight than those without a family history of T2D.[15]

- ***Intensive insulin therapy:*** Although insulin is essential for controlling glucose and preventing diabetes complications, it can promote increased caloric intake or conserve ingested calories, leading to weight gain.[16-19] Another theory suggests that administering insulin peripherally bypasses the effects on the liver, which can potentially cause hyperinsulinemia and fat accumulation in peripheral tissues.[18,19] Other pathways explaining insulin-induced weight gain have been proposed, including alterations to the growth hormone or insulin-like growth factor 1 (IGF-1) system. This system plays a key role in maintaining body composition by delicately balancing anabolism and catabolism.[20,21]

- ***Age and duration of diabetes:*** In a retrospective observational cohort study of children and adolescents with T1D (aged 0–18 years), weight gain was linked to both age and the duration of T1D. This association could be a result of prolonged and intensive insulin use following diagnosis.[22]

- ***Fear of hypoglycemia:*** In the DCCT, the risk of severe hypoglycemia was increased threefold in individuals treated with intensive insulin therapy compared to those on conventional therapy.[19] Weight gain in individuals with T1D can be attributed to defensive snacking to prevent exercise-related hypoglycemia or consuming extra carbohydrates to counter hypoglycemia. While the use of insulin analogues has reduced the risk of hypoglycemia, it remains the most common acute complication of T1D.[23] Automated insulin delivery (AID) systems could potentially decrease the frequency of hypoglycemia by better-matching insulin delivery with glucose levels. However, the current use of these systems is limited, and it is uncertain whether they will significantly reduce defensive snacking and weight gain.[24] Fear of hypoglycemia during exercise could be a key factor contributing to weight gain in individuals with T1D. Data from accelerometers in adults newly diagnosed with T1D indicated lower moderate-vigorous physical activity levels than those for adults without T1D. Nevertheless, these findings were not comprehensive.[25] Education on adjusting insulin doses with physical activity is essential for individuals with T1D, because without this knowledge some may be discouraged from exercising, potentially contributing to weight management issues.[26–28]

- ***Insulin resistance***: OB in individuals with T1D can lead to IR, resulting in a condition known as "double diabetes," which can complicate the management of T1D.[29,30] IR can also occur independently of weight in individuals with T1D.[31] The cause of this IR could be linked to the external delivery of insulin, and it manifests with a unique phenotype associated with abnormal physiological outcomes, regardless of weight.

Complications of Obesity in Individuals with Type 1 Diabetes:

Long-term data on OB in individuals with T1D is currently limited. However, it is reasonable to assume that OW and OB may have more severe effects on this group of individuals than on the general population. High BMI was associated with an increased risk of major cardiovascular disease, heart failure, cardiovascular death, and mortality in individuals with T1D, especially in men.[6] IR in individuals with T1D has significant implications and has been linked to a higher risk of microvascular complications.[32,33] Additionally, studies suggest a connection between excess adiposity, IR, and

coronary artery calcification, with cardiovascular disease being the leading cause of death in adults with T1D.[34,35]

Treatment Strategies For Managing Obesity in Individuals with T1D

Managing OB in individuals with T1D requires a delicate balance between optimizing glycemic control and achieving sustainable weight loss. Several treatment modalities have been explored, including lifestyle interventions, pharmacologic approaches, and surgical procedures.

1. Lifestyle and behavioural modifications

The treatment of OB is complex and must involve a multidisciplinary approach, including lifestyle and behavioural modifications (e.g., diet and physical activity), which constitute the backbone of OB management in general. Dietary adjustments, physical activity, and behavioural therapy are essential for promoting weight loss while maintaining glycemic control.

Dietary modifications: Lifestyle changes are not just beneficial, but they are also the key to success in managing obesity in individuals with T1D. The most effective strategy is a high-intensity dietary program with frequent contact with individuals, which has the potential to result in an average weight loss of approximately 5–10%.[36] However, maintaining weight loss over time is challenging for most individuals.

Many diets can lead to weight loss in individuals with OW or OB, such as the Mediterranean diet, plant-based or vegetarian diet, or low carbohydrate diet. There is inadequate research in T1D to support one diet over another.[37-40] The specific breakdown of macronutrients in a diet seems to have less effect on weight loss than adherence to the diet. Therefore, any diet plan should be tailored to the individual's clinical characteristics and preferences, emphasizing the importance of personalized care. This approach should be designed to improve long-term adherence, which is crucial for successful weight management. Therefore, the presence of a dietitian in the multidisciplinary team is essential.[38]

The primary focus of any OB dietary program, with or without diabetes, is to decrease overall caloric intake. A reduction of 500–1000 kcal per day or 25–30% of daily caloric intake can result in a weight loss of 0.5 kg to 1 kg per week, equivalent to more than a 5% weight loss over an average period of 6 months. For individuals with T1D, it is essential to promote the consumption of carbohydrates with a low glycemic index and high fibre content sourced from vegetables, legumes, fruits, and whole grains. These high-fibre foods play a crucial role in the diet, providing a sense of fullness and aiding in digestion, empowering individuals to make informed dietary choices. It is also important to avoid added sugar, refined carbohydrates, and highly processed foods.[38-40]

The current ADA guidelines recommend no specific macronutrient composition of meal plans for individuals with T1D but emphasize the importance of balancing the insulin dose with the carbohydrate content.[40] However, special attention should be given to the evidence surrounding low carbohydrate (<130 g carbohydrate/day) and ketogenic diets (<55 g carbohydrate/day) for individuals with T1D. While these diets are popular for weight loss in individuals with OB and T2D, there is limited evidence of their effectiveness for individuals with T1D, and concerns have been raised about the risks of hypoglycemia and diabetic ketoacidosis (DKA).[41] For instance, a low carbohydrate diet may reduce hepatic glycogen stores, thereby impairing the effect of glucagon in the event of hypoglycemia. A study on individuals with insulin pump–treated T1D found that a low carbohydrate diet (<50 g/day) attenuated the glycemic response to a subcutaneous glucagon bolus compared to a high carbohydrate diet.[42]

The effectiveness and safety of intermittent fasting for individuals with T1D have not been proven. Therefore, proper training and adjustments to insulin doses are essential to prevent hypoglycemia.

Physical activity: Regular physical activity has numerous benefits, including weight management, reducing the risk of cardiovascular disease and mortality, improving dyslipidemia, and enhancing mental health outcomes.[43,44] For individuals with T2D, physical activity can improve IR, reduce insulin dose requirements, and limit insulin-associated weight gain. However, individuals with T1D may face an increased risk of hypoglycemia with physical activity, leading to fewer than 5% of adolescents with T1D meeting the pediatric clinical guidelines for physical activity.[45] The development of AID systems may allow for a more individualized approach and make exercising safer by preventing hypoglycemia and providing a better balance between glucose levels and insulin administration.

Behavioural therapy: It is common for individuals with OB and T1D to experience psychosocial challenges that need to be identified and addressed effectively. These challenges include

fear of hypoglycemia, diabetes distress, anxiety, depression, lack of support, low self-esteem, and the stress of managing a chronic illness. Additionally, eating disorders are estimated at approximately 7% among individuals with T1D.[46]

Integrating psychological assessment and behavioural therapy into the standard clinical care for OB in individuals with T1D is essential. This should involve setting achievable goals, self-monitoring food intake and exercise, problem-solving strategies, developing coping skills, controlling environmental triggers, stress management, education, and, most importantly, social support. These behavioural interventions are beneficial when part of a structured weight management program.[36]

2. Pharmacological interventions

The interaction between insulin, appetite control, and weight gain in individuals with T1D is intricate. Using medication alongside lifestyle changes can be helpful in addressing OB in individuals with T1D.

A. Anti-obesity medications:

Patients who do not achieve significant weight loss with lifestyle changes may be considered for anti-OB medications. According to current guidelines, anti-OB medications can be considered for individuals with a BMI of 30 kg/m^2 or higher or a BMI of 27 kg/m^2 or higher with OB-related complications, in addition to lifestyle modifications.[47,48] Food and Drug administration (FDA)-approved long-term anti-OB medications include Orlistat, Naltrexone-Bupropion combination, Pheteramine-Topiramate combination, Liraglutide at a dose of 3 mg, Semaglutide at a dose of 2.4 mg, and Tirzepatide, while Phentermine is approved for short-term use only.[49,50] While there is limited data on the use of these medications in individuals with T1D due to their exclusion from major trials, it is reasonable to assume that individuals with OB and T1D may benefit from these drugs in practical settings. The exclusion of T1D from clinical trials for pharmacological obesity management introduces bias and exacerbates discrimination against these patients due to their OB.

B. Glucose-lowering agents as adjuncts to insulin treatment in T1D:

Amylin analogs (e.g., Pramlintide): Amylin is a hormone that is co-secreted with insulin from pancreatic beta cells. Pramlintide, a synthetic amylin analog, is the only adjuvant therapy for T1D approved by the FDA.[51] It has been shown to improve long-term glycaemic control and induce an average weight loss of 0.4–1.3 kg compared to an average weight gain of 0.8–1.2 kg in the placebo group.[52,53]

Metformin: Metformin has been traditionally used to treat individuals with T2D, but it has also been studied as an adjunct treatment for individuals with T1D, especially those with OB and IR. Metformin works by reducing the production of glucose in the liver, enhancing the body's sensitivity to insulin in the peripheral tissues, and decreasing the absorption of glucose, which can result in a slight reduction in weight and lower insulin requirements.[54] Some clinical trials involving a small number of participants with T1D have looked into the effects of adding metformin to insulin compared to adding a placebo. These trials have shown a decrease in insulin doses (ranging from -5.7 to -8.8 units per day) and a decrease in weight (ranging from -1.74 kg to -3.8 kg) with no impact on hemoglobin A1c (HbA1c) levels.[47,55] The REMOVAL trial involved 428 patients with T1D who were randomly assigned to receive either metformin or a placebo.[48] The trial measured the progression of common carotid artery intima-media-thickness (cIMT) as an indicator of atherosclerosis. The results showed a reduction in body weight by 1.17 kg but no decrease in HbA1c levels, insulin requirements, progression of mean cIMT, or increase in hypoglycemia compared to the placebo.[48]

Dipeptidyl peptidase-4 (DPP-4) inhibitors: The DPP-4 inhibitors work by increasing the levels of endogenous glucagon-like peptide 1 (GLP1) by inhibiting its metabolism by the enzyme DPP-4. This rise in GLP1 levels leads to a reduction in glucagon and an increase in insulin secretion in a glucose-dependent manner. In individuals with T1D, there is a contradictory increase in glucagon levels, which is associated with post-meal glucose levels.[56] Sitagliptin is the sole DPP-4 inhibitor examined in individuals with T1D, and it has not led to any significant weight loss.[57,58]

GLP-1 Receptor Agonists: GLP-1 receptor agonists are frequently used to treat individuals with T2D and have been shown to effectively reduce weight by decreasing appetite, increasing a feeling of fullness, and slowing down the emptying of the stomach.[59] These medications may also be beneficial for individuals with OB and T1D, leading to weight loss and reduced insulin requirements without increasing the risk of severe hypoglycemia.

Liraglutide and exenatide were the only GLP-1 agonists studied extensively in individuals with

T1D.[60] Lixisinetide and albiglutide were each studied in a single study.[60] A recent meta-analysis included 24 studies using 4 different GLP-1 analogues with 3377 patients.[60] Liraglutide had the most substantial evidence, with an estimated weight loss of −4.89 kg for the 1.8 mg dose, −3.77 kg for the 1.2 mg dose, and −2.27 kg for the 0.6–0.9 mg dose. The estimated weight loss was −4.06 kg for exenatide. As expected, GLP-1 agonist treatment was associated with more gastrointestinal side effects, but it did not significantly increase the risk of DKA, or symptomatic or severe hypoglycemia.[60]

Semaglutide has been evaluated in some observational trials involving individuals with T1D. It resulted in an average weight loss of 7.23–8.8 kg (7.6–10.6%), and improved HbA1c and time in range (TIR) without increasing the risk of hypoglycemia or DKA.[61-64]

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist that has been shown to reduce weight in individuals with T2D and OB.[49,50,59] It has been studied in individuals with T1D in 2 observational studies. The first study included 26 patients and revealed a significant reduction in body weight by 3.4%, 10.5%, and 10.1% at 3, 6, and 8 months after starting tirzepatide, respectively, that was accompanied by improved HbA1c and TIR.[65] The other study included 62 patients with T1D and OW or OB matched with 37 control participants.[66] Tirzepatide resulted in an average weight loss of 21 kg (18.5%) at one year, with a significant improvement in HbA1c and TIR.[66]

SGLT2 inhibitors: SGLT2 inhibitors increase urinary glucose excretion, which helps improve glycemic control and results in modest weight loss.[59] However, only a few studies have evaluated their use in individuals with T1D.

Dapagliflozin: In the DEPICT-1 and DEPICT-2 trials, patients who were given dapagliflozin 5 mg or dapagliflozin 10 mg experienced a significant reduction in body weight (ranging from -2.95% to -4.54% compared to placebo), as well as a decrease in HbA1c levels (-0.33% to -0.37% with dapagliflozin 5 mg and -0.36% to -0.42% with dapagliflozin 10 mg) and insulin dosage. The rates of hypoglycemia did not differ, but the incidence of DKA was higher in the treatment groups (2.6% to 4% with dapagliflozin 5 mg, 2.2% to 3.4% with dapagliflozin 10 mg, and 0% to 1.9% with placebo).[67,68]

Empagliflozin: In the EASE-1 trial, patients were randomly assigned to receive empagliflozin at a dose of 10 mg, 25 mg, or a placebo. In the EASE-2 and EASE-3 trials, patients were randomized to receive empagliflozin at doses of 2.5 mg, 10 mg, 25 mg, or a placebo.[69,70] Across all trials, empagliflozin was associated with a significant reduction in weight (-1.5 kg to -3.6 kg) and HbA1c levels compared to the placebo. Additionally, the insulin dose was also decreased. However, higher rates of DKA were observed in patients receiving higher doses of empagliflozin (10 mg and 25 mg). Specifically, the rates of DKA were 0.8% with empagliflozin 5 mg, 4.3% with empagliflozin 10 mg, 3.3% with empagliflozin 25 mg, and 1.2% with placebo.[70]

Sotagliflozin (combined SGLT1 and SGLT2 inhibitor): The inTandem program assessed the effectiveness and safety of using sotagliflozin in individuals with T1D.[71-73] The 3 trials demonstrated a decrease in weight (-1.98 kg to -4.34 kg), HbA1c levels (-0.21% to -0.46%), and insulin dosage. The incidence of documented hypoglycemia was lower, but there were more gastrointestinal adverse events in the sotagliflozin group. The DKA rate was higher in patients treated with sotagliflozin (3.4% with sotagliflozin 200 mg, 4.2% with sotagliflozin 400 mg, and 0.4% with placebo).

When considering SGLT2 inhibitors for those with T1D, it is crucial to carefully select patients and closely monitor them. In randomized controlled trials, the increased risk of DKA has limited the approval of SGLT-2 inhibitors for individuals with T1D. Dapagliflozin was approved by the European Drug Agency (EDA). However, in October 2021, the manufacturing company voluntarily removed the T1D indication for dapagliflozin after recommendations from UK and EU medicines regulators to add an inverted black triangle to the label to indicate the need for additional monitoring when prescribing this drug.[74]

3. Metabolic surgery

Most studies evaluating the effect of metabolic surgery in individuals with T1D are limited by the small sample size and inclusion of different types of surgeries. They mainly focused on weight loss and insulin use. Additionally, long-term follow-up is lacking, and side effects have not been systematically reported.

The most extensive study evaluating metabolic surgery in patients with T1D is a register-based nationwide cohort study from Sweden.[75] Individuals with T1D and obesity who underwent Roux-en-Y gastric bypass (RYGB) surgery were compared with patients with T1D and OB who were matched for age, sex, BMI, and calendar time who did not undergo surgery. A total of 387 individuals who had

undergone RYGB and 387 control patients were identified and followed for 9 years. The participants' weight was reduced by 25% at 1 year and 29% at 2 years after surgery compared to 5% at 1 and 2 years in the control group. HbA1c decreased by 1% at 1 year and 0.8% at 2 years after surgery compared to no change in the control group. The analysis also showed a lower risk for cardiovascular disease, cardiovascular death, hospitalization for heart failure, and stroke for the RYGB group. There was a higher risk for serious hyperglycemic events and substance abuse after surgery.

A systematic review that included 30 studies with 706 patients revealed a mean excess weight loss of 74.57% at ≥6 follow-up months.[76] The most common procedure performed was RYGB (n = 497, 70.4%), followed by SG (n = 131, 18.6%). The insulin dose was reduced from a mean of 92.3 IU/day preoperatively to a mean of 35.8 IU/day post-operatively. No significant trends were found for changes in HbA1c levels. Reductions in comorbidities such as hypertension and cardiovascular disease were recorded in multiple studies. The main side effects were episodes of hypoglycemia and DKA, and there was no mortality.

In summary, the use of metabolic surgery in T1D patients with severe OB has been shown to effectively reduce weight and insulin dosage while improving OB-related conditions such as hypertension, dyslipidemia, and obstructive sleep apnea. Recent studies indicate a significant decrease in cardiovascular disease and mortality. Despite the observed adverse events, such as an elevated risk of hypoglycemia and DKA, the benefits of this approach outweigh the drawbacks. However, it is crucial for these patients to receive close monitoring from a multidisciplinary team to ensure a personalized and adjustable insulin regimen throughout all stages of treatment, in addition to diabetes care and education. New diabetes technologies, including real-time continuous glucose monitoring and AID systems, may offer valuable support in this scenario.

Conclusion and Future Directions

Obesity in individuals with T1D is a challenging and rapidly growing health issue. It significantly affects glycemic control and increases the risk of long-term complications. A comprehensive approach to treatment, including lifestyle changes, medication, and, in some cases, metabolic surgery, is crucial for achieving weight loss and improving metabolic outcomes in these patients. Providing extensive education and support to help individuals match insulin doses to food intake and exercise is fundamental in managing both weight and sugar levels in these individuals.

While existing evidence highlights the concern of undesired weight gain in treating individuals with T1D, high-quality data on this topic is limited. Further research is needed to understand the full impact of OB on the overall health of individuals with T1D. Future treatments and technologies should not only focus on enhancing glucose control but also on facilitating weight management. It is equally important to explore adjunct therapies that can improve glycemic control through insulin-independent pathways, as these could offer new avenues for treatment.

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Glucagon-like Peptide Receptor Agonists (GLP-1 receptor agonists): A Powerful Addition to Foundational Therapy Kidney Care in Patients with Type 2 Diabetes Mellitus

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Current State of Therapy in CKD with Type 2 Diabetes Mellitus

There has been a veritable explosion in therapeutic options for patients with chronic kidney disease (CKD) and Type 2 diabetes mellitus (T2DM). For the past several decades, therapy for this condition has been limited to glycemic control, blood pressure control and utilization of angiotensin converting enzyme inhibitors (ACEi's) or angiotensin 2 receptor blockers (ARBs). Recently, the emergence of therapies with organ protective effects has completely altered the landscape of therapy and outcomes for CKD in T2DM.[1] Specifically, several large randomized clinical trials have demonstrated the positive impact of sodium glucose luminal transporter 2(SGLT2) inhibitors on the progression of kidney disease, end-stage kidney disease (ESKD), major adverse cardiovascular events (MACE), cardiovascular (CV) death, hospitalization for heart failure(HHF), all-cause hospitalization, and all-cause mortality.[2] Furthermore, finerenone, a non-steroidal mineralocorticoid receptor (nsMRA), has also been established as a component of foundational kidney therapy in patients with T2DM.[3] A robust clinical trial program demonstrated kidney protection, CV protection and reductions in HHF in patients with CKD and T2DM. International guidelines have been updated to incorporate these agents as standards of care in this group of patients.[4] CKD in T2DM is a complex disease and it stands to reason that multi-targeted therapy could result in better outcomes for patients, similar to the management of patients with chronic heart failure.[1] Those who follow this field will have noted that GLP-1 receptor agonists are listed as a component of guideline-directed management. However, these recommendations are based on the CV protective

effect of these agents.[4] Until recently, it was not clear if GLP-1RA's possessed kidney protective properties. The recent publication of the FLOW trial confirms that GLP-1 receptor agonists are, in fact, kidney protective.[5]

Mechanisms Contributing to the Pathogenesis of CKD in T2DM

The development of kidney disease in patients with T2DM is quite complex. The ensuing discussion will focus on diabetic nephropathy (DN). It is, however, important to recognize that patients with T2DM may develop other kidney diseases apart from DN. For example, patients with T2DM often have overlapping risk factors for small vessel ischemic renovascular disease and may manifest this condition.[6]

Given that dysglycemia is a requirement for the development and progression of DN, not surprisingly, there are metabolic factors that influence DN. First, the advanced glycation end products and glucose metabolism by-products lead to several disturbances, including endothelial dysfunction, dysregulated angiogenesis (similar to diabetic retinopathy), dysregulated cell growth, and the generation of reactive oxygen species. These deleterious alterations have been associated with the development of tissue fibrosis and vascular disease in the kidney. Second, there is evidence to demonstrate that various growth factors become over-expressed, including vascular endothelial growth factor, which leads to abnormal angiogenesis. Third, there are hemodynamic factors that contribute to kidney disease progression in T2DM. These hemodynamic perturbations include systemic hypertension and intraglomerular hypertension. Intraglomerular hypertension appears to be a terminal pathway of many kidney diseases, including DN. It leads to progressive glomerular sclerosis and its development is heralded by albuminuria.[6] It remains an important clinical practice point to highlight that care providers must order an assessment of albuminuria when screening patients with T2DM for CKD. Not only is it an earlier marker of kidney disease when compared with eGFR, but it also portends much worse kidney and CV outcomes. The identification of albuminuria also represents an opportunity for meaningful therapeutic intervention. Many of the existing therapies for CKD in T2DM target intraglomerular hypertension, including ACEi's/ARBs, SGLT2 inhibitors, and finerenone.[7] Finally, there are several proinflammatory and profibrotic factors that lead to kidney inflammation and fibrosis. Clearly, this is a complex interaction of pathogenic processes, and this may explain why multi-targeted therapy is required to best address CKD in T2DM.[6]

GLP-1 receptor agonists have many potential mechanisms that address the pathogenesis of kidney disease in T2DM, and these mechanisms appear to complement other therapies in this space (**Figure 1**). GLP-1 receptor agonists are powerful anti-hyperglycemic agents and additionally have powerful weight loss properties well suited to addressing the derangements caused by AGE's and glucose metabolism byproducts. Additionally, GLP-1 receptor agonists appear to stimulate pathways in the kidney that enable degradation of reactive oxygen species. Both basic science and human research have demonstrated the anti-atherosclerotic properties of this class of medication. It has become apparent that obesity itself can result in kidney disease and there is emerging research to suggest that perinephric fat may result in maladaptive hormone signalling, resulting in negative kidney impacts. Thus, the weight loss properties of these agents could have added an independent benefit in overweight patients. Regarding hemodynamic perturbations, GLP-1 receptor agonists have been shown to reduce systemic blood pressure by approximately 2.2 mmHg. Perhaps, surprisingly, GLP-1 receptor agonists also possess a natriuretic effect that not only reduces blood pressure but may also favourably regulate intraglomerular hypertension. This is thought to be mediated by sodium hydrogen exchanger 3. Interestingly, SGLT2 inhibitors are also thought to interact with this exchanger. The inflammation associated with kidney disease in T2DM may also be at least partially addressed by GLP-1 receptor agonists. Research in this area indicates that GLP-1 receptor agonists downregulate various inflammatory cytokines and prevent the infiltration of inflammatory cells into the kidney.[1] Certainly, this is a various complex area, but GLP-1 receptor agonists have multiple mechanisms that make them well suited to treat kidney disease in T2DM and these mechanisms are likely complemented by other therapies for this condition.

Efficacy of GLP-1 receptor agonists

Cardiovascular protection

Patients with CKD in T2DM are at very high risk of CV disease and this is often their most common cause of mortality. Both clinical trials and

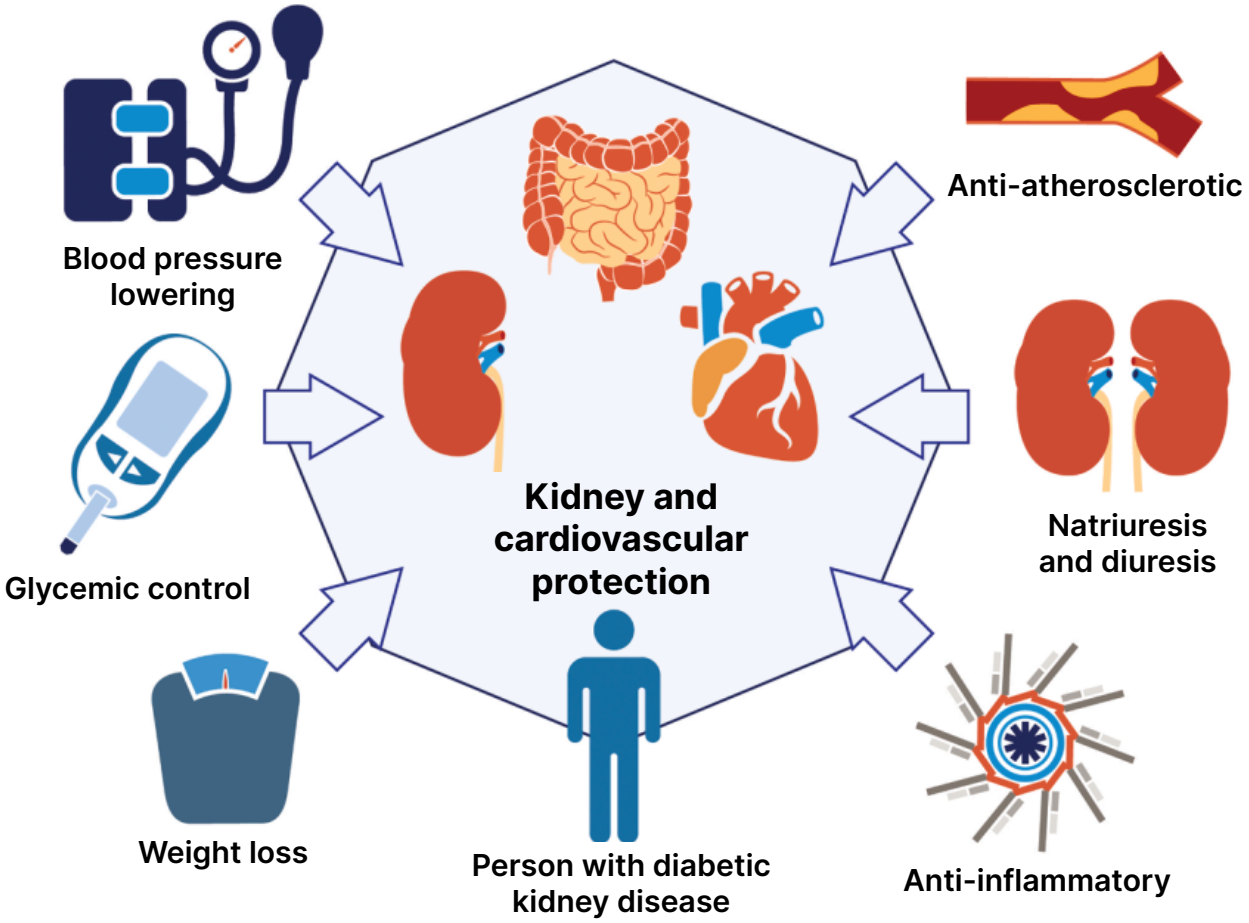

Figure 1. Potential mechanisms by which GLP1-RA confer kidney and cardiovascular protection; *adapted from Michos ED, et al., 2023.*

epidemiologic data indicate that having moderate CKD and albuminuria increases a patient's risk of CV disease by 50%, even in the context of T2DM, which is already a high-risk condition.[8] Albuminuria accounts for a large portion of this risk and beyond predicting the risk of CKD progression and CV disease, it also predicts the development of new HF and worse outcomes for patients with established HF.[9] Therefore, it is important to not only address the risk of progressive CKD, but also, if possible, reduce CV risk. In addition to SGLT2 inhibitors and finerenone, GLP-1 receptor agonists reduce CV risk in many populations, including those with CKD. A meta-analysis of CV outcome trials (CVOT's) from 2021 revealed a 17% (HR 0.83; 0.74–0.93) relative risk reduction in MACE events for patients with an eGFR <60. This data led to the inclusion of GLP-1 receptor agonists in international guidelines.[10] Additionally, GLP-1 receptor agonists have been shown safe in patients with lower GFRs (>15), have low rates of hypoglycemia, are effective at reducing HbA1C, and result in beneficial metabolic benefits, including weight loss.[1]

Kidney protection

A meta-analysis of secondary kidney outcomes from large CVOT's with GLP1-RA therapy demonstrated a reduction in albuminuria but failed to demonstrate statistically significant eGFR preservation. However, the point estimate (HR 0.86; 0.72–1.02) suggested that a reduction in eGFR decline was possible.[10] Therefore, the FLOW trial was conceived and recently completed to definitively examine the effects of semaglutide on kidney function in patients with CKD in T2DM. This trial enrolled 3533 participants with T2DM , an eGFR of 25–75 and albuminuria to be randomized to receive semaglutide in addition to standard of care vs. placebo. The primary outcome of the trial was a composite of kidney failure (ESKD, transplantation, or eGFR <15), a 50% reduction in eGFR from

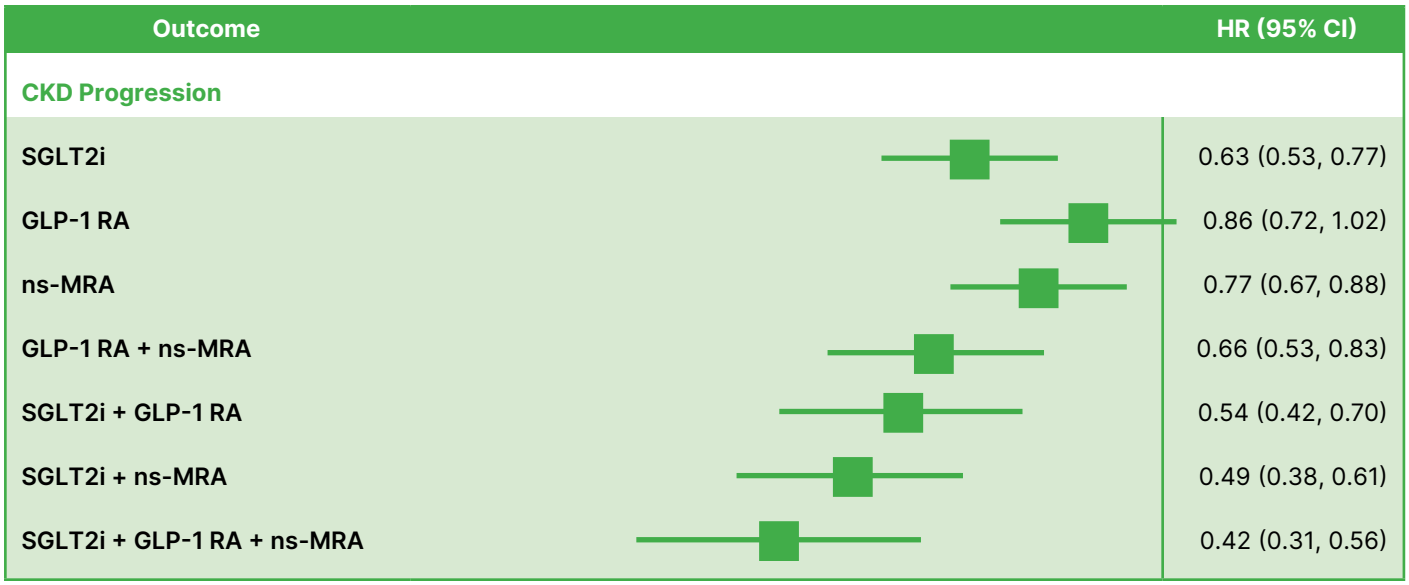

Figure 2. Estimated treatment effects on CKD progression of SGLT2i, GLP-1RA, and ns-MRA, alone and in combination, when added to renin-angiotensin system blockage in patients with type 2 diabetes; adapted from Neuen, BL, et al., 2024.

baseline, kidney-related death, or CV death. Notably, this outcome did not include albuminuria. Greater than 95% of the cohort were on ACEi or ARB therapy. This landmark, first kidney outcome trial of GLP-1 receptor agonists confirmed that semaglutide is a kidney protective agent with 23% (HR 0.76; 0.66–0.88) relative risk reduction in the primary outcome. Given that GLP-1 receptor agonists are known to be CV protective, the primary outcome was converted to a kidney-specific outcome by removing CV death from the analysis and this kidney-specific outcome remained statistically significant in favour of semaglutide (HR 0.79; 0.66–0.94). Additionally, eGFR slope was preserved by 1.16 mL/min/year, which is significant.[5] To put this into context, ACEi's or ARBs have a 0.75–1.0 mL/min/year preservation of eGFR slope. A preservation of 0.75 mL/min/year is accepted as a surrogate for delaying ESKD.[11,12] Therefore, this trial confirms that semaglutide is kidney protective and that GLP-1 receptor agonists should be prioritized for patients with CKD in T2DM and risk factors for CV disease. Reassuringly, the FLOW trial also demonstrated important and significant reduction in CV death, MACE and all-cause mortality in this high-risk kidney group.[5]

Conclusion

As clinicians, we have entered the HF realm where we have 4 evidence based pillars of care for CKD therapy in T2DM. It is incumbent upon the community of care providers (primary care, diabetes educators, nurses, pharmacists, and specialists) to pursue the implementation of guidelines to direct quadruple therapy (ACE/ARB, SGLT2 inhibitor, nsMRA and GLP-1 receptor agonist) in all patients with CKD and T2DM where indicated. Recent modelling analyses suggest that combination therapy has meaningful and sequential reductions in kidney, CV and mortality outcomes (**Figure 2**).[13] Furthermore, a recent meta-analysis of the landmark trial in T2DM indicates that addition of an SGLT2 inhibitor in the presence or absence of GLP-1 receptor agonist therapy has the same beneficial effects on these outcomes.[14] This means that current data suggests that the effects of these therapies are not diminished when added to other outcomes reducing agents as background therapy. Care providers often have questions about the sequencing of these therapies. However, this is likely not as important as ultimately initiating patients on guideline-directed medical therapy for CKD.[15] Patient and clinical priorities may also dictate this sequence. For example, if a patient is quite dysglycemic, GLP-1 receptor agonist and SGLT2 inhibitor therapy may be prioritized. If the patient is primarily concerned with weight loss, a GLP-1 receptor agonist would likely be added sooner. Therefore, tailoring of individualized approaches for patients may result in better success and compliance with the delivery of this package of care. As an easy reminder, if a patient has residual albuminuria, this represents an opportunity to add additional therapies to further reduce the patient's kidney risk.

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Monogenic and Syndromic Obesity: Therapeutic Implications

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Introduction

Obesity is a complex, progressive and relapsing neuroendocrine condition, characterized by disordered communication between the gastrointestinal tract, adipocytes and the hypothalamus.[1] It is a heterogeneous condition with unique etiologies, broadly classified as: polygenic obesity, monogenic obesity, syndromic obesity and secondary obesity.[2] The most common form of obesity is polygenic, a highly hereditable condition that involves the clustering of genes that increase the risk for obesity. This inherited genetic risk is exploited by socio-biologic exposures.[1] Monogenic and syndromic obesity result from rare genetic mutations and are characterized by early onset severe obesity and hyperphagia.[3] Secondary obesity may occur as a result of medication exposures, hypothalamic damage or primary endocrine disorders.[4] Accurate classification of obesity is critical to inform surveillance and management strategies, decrease health risk and improve quality of life through newly available targeted therapies.[4]

Recognizing Monogenic and Syndromic Obesity

Monogenic and syndromic forms of obesity are caused by mutations in genes involved in the neuroendocrine control of body weight. They result in early onset and severe obesity (BMI Class II, III) with rapid weight gain typically within the first 2 years of life and Class II, III obesity by age 5. They have associated hyperphagia and impaired satiety. They may have neurodevelopmental differences, unique physical features and/or associated endocrinopathies. Although syndromic obesity is more often associated with developmental delay, dysmorphic features and multisystem involvement than monogenic obesity, this is not exclusive. While these conditions are rare, there is concern that they are under-recognized since consideration of genetic testing in those living with severe obesity remains low.[5] Monogenic and syndromic forms of obesity are typically resistant to weight management strategies including low responsiveness to traditional anti-obesity medications and metabolic bariatric surgery. While the onset of symptoms begins early in life, adults living with these rare forms of obesity may have

never been assessed or investigated, leading to missed therapeutic opportunities that could be life changing.[6] Hyperphagia in these conditions is a result of genetic mutations that lead to heightened and unrelenting feelings of hunger. It takes a longer time and larger volumes of food to sense satiety and feelings of satiety are short lived. Thoughts of food are often intrusive and all-encompassing, leading to food seeking, food foraging, night time eating, and high distress if food is unavailable or restricted. High food pre-occupation can interfere with focus, concentration, task completion, education, and employment attainment. Hyperphagia can have a negative impact on quality of life for both the person living with the condition and their caregivers, and can interfere with peer and family relationships.[7]

The risk for weight-related health complications among people living with monogenic and syndromic obesity is high, given the early onset and severity of the obesity with which they live. This includes cardiometabolic health risk, biomechanical health complications and psychosocial challenges.[8] Co-existing neurodevelopmental challenges can also present as barriers to accessing and engaging weight management support.[9] The consequences of severe obesity are often the primary cause of shortened life expectancy in these forms of obesity.[10]

Disorders of leptin and melanocortin 4 Receptor (MC4R) signalling are responsible for many of these conditions. The availability of the MC4R agonist setmelanotide has allowed people living with a subset of these rare forms of obesity much-needed support in the management of their associated hyperphagia and body weight.

The Role of Leptin and MC4R Signalling in Body Weight Regulation

Leptin is secreted by adipocytes and acts as our main signal of nutritional status (**Table 1**).[11] Leptin signalling promotes satiety and energy expenditure. Leptin binds to the leptin receptor at the level of the ventromedial hypothalamus to stimulate production of proopiomelanocortin (POMC), which is subsequently cleaved by the enzyme PCSK1 to ACTH and alpha MSH. Alpha MSH binds to MC4R to transmit the signal of satiety or fullness and impact energy expenditure. Leptin signalling is enhanced by SH2B1, an adaptor signalling protein, which is also involved in peripheral insulin signalling. Rare genetic mutations within this pathway including genes encoding MC4R, POMC, PCSK1, leptin receptor, leptin, and SH2B1, as well as those associated with Bardet Biedl Syndrome (BBS), Alstrom Syndrome, Albright osteodystrophy, and Prader Willi Syndrome have been identified. Disruption of signalling through this pathway leads to hyperphagia and early onset severe obesity.[12]

Disorders of leptin signalling can also lead to short stature, delayed puberty, hypothyroidism, emotional lability, behavioural difficulties, intellectual disabilities, and altered immune function.[12]

Clinical Characteristics of Monogenic and Syndromic Forms of Obesity

Syndromic obesity is associated with early onset obesity and other clinical manifestations that involve multiple systems, including neurodevelopment, physical features, congenital malformations, and other organ involvement. The most common obesity syndromes, including Prader Willi Syndrome, Bardet Biedl Syndrome, Alstrom Syndrome, and Albright osteodystrophy have co-occurring hypothalamic dysfunction.

Monogenic forms of obesity present with very early onset and rapid weight gain, most often within the first 2 years of life. Cognitive development is often normal, although not exclusively. Some monogenic forms of obesity are associated with endocrinopathies, most commonly hypogonadism, but may also include thyroid dysfunction, adrenal insufficiency, hyperinsulinemia, and tall or short stature. These individuals may have unique physical features (pale skin, red hair), higher risk for infection, transient neonatal malabsorptive diarrhea and/or cholestasis.

Assessment and Management

Clinical practice guidelines recommend assessment for possible monogenic or syndromic forms of obesity in children with severe obesity (BMI Class II, >120% of the 95th percentile OR >35 kg/m^2) before age 5 years, with hyperphagia and/or a family history of severe obesity.[4] Diagnostic gene panels or exome-based sequencing are recommended. If there are coexisting features of syndromic causes such as developmental delay, unique physical features, vision loss or renal impairment, genetic tests targeting the suspected syndromic form of obesity should be considered.

Management should include an interdisciplinary team with expertise in weight management, neurodevelopment and behaviour. Behavioural approaches to hyperphagia are very challenging and may include securing the home food environment

Condition/Gene	Hyperphagia	Clinical features	Endocrinopathies	Targeted therapy
Monogenic Obesity				
Leptin Deficiency	+++	Onset of obesity within the first few months of life; increased risk for infection	Hypogonadism Hypothyroidism Short stature	Metreleptin
Leptin Receptor Deficiency	+++	As above; less frequent recurrent infections	Hypogonadism	MC4R agonist: Setmelanotide
SH2B1 deficiency (mediates leptin signaling centrally and insulin signaling peripherally)	+++	Leptin and insulin resistance; language delays; behavioural difficulties	Insulin resistance Type 2 Diabetes Short stature	MC4R agonist: Setmelanotide
POMC deficiency	+++	Pale skin; red hair; cholestatic jaundice in infancy	ACTH deficiency	MC4R agonist: setmelanotide
PCSK1 deficiency	+++	Neonatal malabsorptive diarrhea	Adrenal insufficiency Postprandial hypoglycemia; hypogonadism Diabetes Insipidus Hypothyroidism	MC4R agonist: setmelanotide
MC4R deficiency * (most common monogenic form of obesity)	+++	n/a	Tall stature; accelerated linear growth; hyperinsulinemia; increased lean muscle and body fat mass	n/a
Obesity Syndromes				
Bardet Biedl Syndrome (ciliopathy; disordered leptin signalling)	++	Polydactyly Visual impairment Structural and/or functional renal abnormalities Intellectual disability	Hypogonadism Truncal obesity	MC4R agonist: setmelanotide
Alstrom Syndrome (Ciliopathy)	++	Progressive visual, hearing and renal impairment Cardiomyopathy	Insulin resistance Truncal obesity; early adrenarche; advanced bone age	n/a
Albright Hereditary Osteodystrophy (GNAS mutation; impaired MC4R signalling)	++	Round faces Short 4th and 5th metacarpal and metatarsal bones; subcutaneous ossifications	PTH; TSH; LH/FSH resistance Short stature	n/a
Prader Willi Syndrome (increased ghrelin; PCSK1 impairment)	++ (onset age 2 y)	Neonatal hypotonia; global developmental delay	Hypothalamic dysfunction; growth hormone deficiency; hypogonadism; high ghrelin; decreased resting energy expenditure	n/a

Table 1. Genetic and clinical characteristics for monogenic and syndromic forms of obesity; *courtesy of Stasia Hadjiyannakis, MD*.

(locks on the refrigerator and pantry) along with constant supervision and limited independence in food preparation, portioning, access, and consumption.[2]

Targeted pharmacotherapy is available for some conditions. Metreleptin, a synthetic analog of leptin, is approved for use in individuals with congenital leptin deficiency. It is administered subcutaneously and can reverse most of the features of this condition.[13,14] Setmelanotide (MC4R agonist) is effective for conditions where MC4R activation is impaired (POMC, PCSK1, SH2B, leptin receptor deficiency, and BBS). In Phase 3 trials 8 of 10 (80%) of those with POMC deficiency, 5 of 11 (45%) of those with LEPR deficiency and 32.2% of those with BBS lost 10% or more of their body weight from baseline.[15-17] Setmelanotide binds to and activates melanocortin receptors and thus helps to decrease symptoms of hyperphagia and increase energy expenditure. It is administered by subcutaneous injection. The most common side effects are hypersensitivity at the injection site and hyperpigmentation of the skin.

The effectiveness of GLP-1 agonists in these conditions is mixed and evidence is limited to case series, reports and open label studies. In individuals with MC4R variants, liraglutide was found to result in 6% weight loss after 16 weeks.[18] In children with Prader Willi Syndrome, there were reported decreases in hyperphagia symptoms but no clinically significant decreases in body weight or BMI.[19,20] Larger randomized control trials are needed to determine whether or not GLP-1 agonists are effective and safe in this patient population. The role of metabolic bariatric surgery is unclear and is most often associated with weight regain over the long term in individuals with monogenic and syndromic forms of obesity (case series).[21-24]

Conclusion

Early recognition, diagnosis and timely intervention for individuals living with monogenic and syndromic forms of obesity can be life changing. It can lead to targeted treatment and surveillance for obesity- and non-obesity-related sequelae and give context to the challenges faced when applying more traditional approaches to weight management. Targeted therapies can also provide some relief from the unrelenting and distressing hyperphagia many of these individuals face. Much of what we learn in the discovery and management of monogenic and syndromic obesity can also inform the understanding and support provided for individuals living with polygenic obesity.

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