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MINI-REVIEW

GLP-1 receptor agonists: the evolution of evidence for fracture risk, body composition, and clinical implications

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Abstract

Older adults, particularly those with diabetes mellitus, are at increased risk of significant functional decline, morbidity, and mortality after fragility fractures. Glucagon-like peptide-1 receptor agonist (GLP-1RA) medications have become increasingly important therapies for diabetes, obesity, and cardiometabolic risk reduction. However, GLP-1RAs appear to exert effects on skeletal health, and this may be clinically relevant in older adults. Recent observational data suggests a modest increase in fracture risk among older adults initiating GLP-1RA therapy, raising concerns about unintended musculoskeletal consequences. Notably, this study specifically looked at fragility fractures as a primary endpoint and was not an incidental safety finding. Potential mechanisms include reduced mechanical loading from weight loss, loss of skeletal muscle mass and bone density, altered bone cellular signaling, decreased nutritional intake, and increased fall risk. Emerging strategies, including clinical trials focusing on pharmacotherapy to address the composition of weight loss and lifestyle interventions, are investigating methods to mitigate unintentional effects of these GLP-1RAs. This mini-review synthesizes the evolving evidence on GLP-1RA medications and skeletal health, explores underlying mechanisms, and outlines clinical strategies to balance the benefits and risks of these therapies.

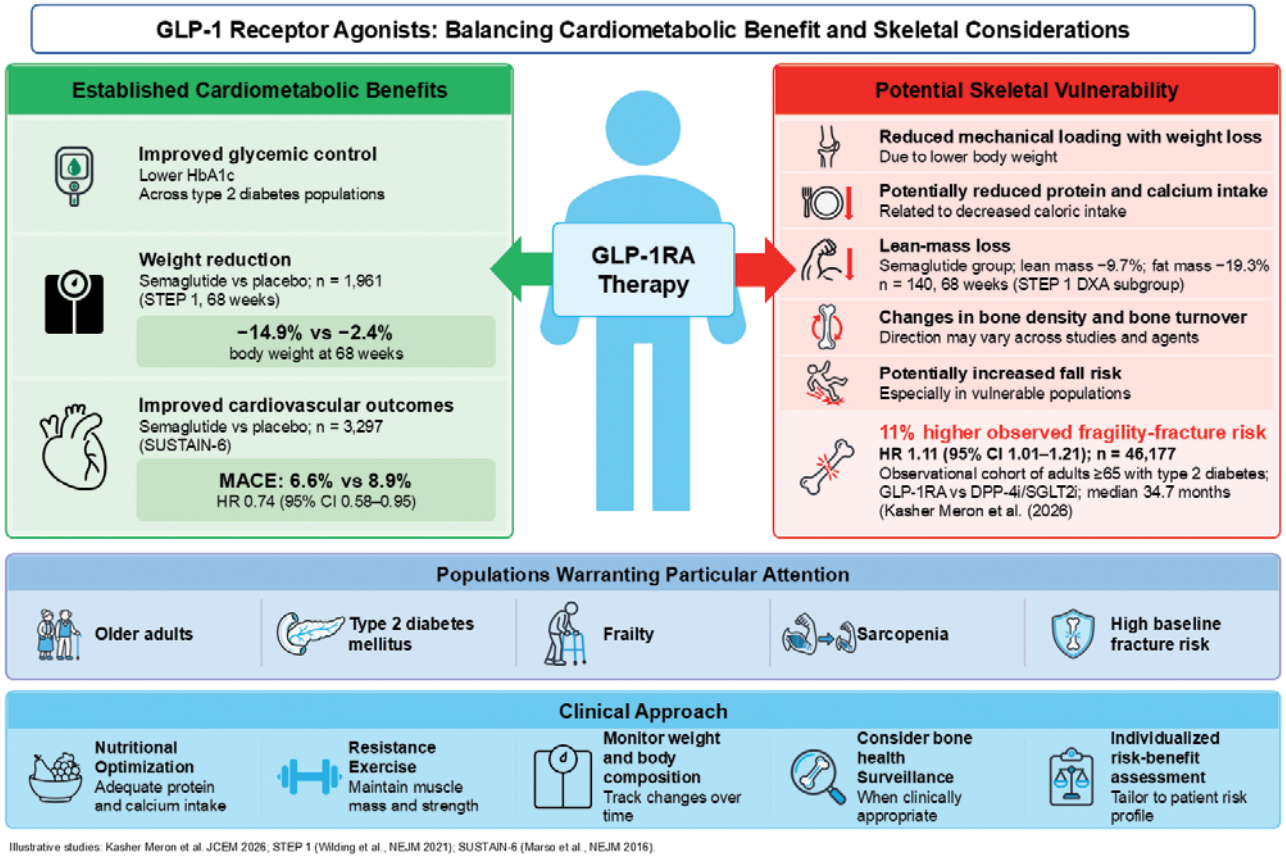
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Graphical abstract



Review

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have become foundational therapies in diabetes mellitus (DM), obesity, and cardiovascular disease. These agents can substantially improve glycemic control, weight reduction, and cardiovascular event outcomes.[1-4] Their expanding use and their study of unintended skeletal health effects have put GLP-1RA medications under more focused attention for long-term safety, including fragility fractures in high-risk populations.

Patients with DM have an increased risk of fragility fractures despite preserved bone mineral density.[5] Measures of trabecular bone scores highlight deficits in bone microarchitecture in those with DM.[6] Importantly, fragility fractures are associated with substantial morbidity, functional decline, and increased mortality, making them clinically significant to study and target for treatment.

Evidence regarding GLP-1RA medications and fracture risk has been mixed but steadily transformed over time. Previously, some trials and analyses have shown negative, neutral, and positive effects.[7-9] However, these studies were limited from the most current context and clinical use of these drugs. Table 1 summarizes the evolution of evidence regarding GLP-1RAs and skeletal health over time.

Early work established that patients with diabetes mellitus have an elevated fracture risk compared to non-diabetics.[4] Factors affecting bone quality and risk of falls contribute to this risk, including sarcopenia.[6,10] Initial randomized controlled trials (RCTs) and other analyses were mixed, but largely neutral with respect to GLP-1RAs on fracture outcomes.[8,9] However, while several studies showed favorable total body weight loss, many of these studies were not designed for skeletal events or had relatively short follow-up durations.[1,12-14] As GLP-1RA use has expanded, modern investigations are addressing this more. Weight loss from these medications is described in terms of the type of weight loss and with a focus on skeletal effects.[15]

Recent, real-world data provides a more current and larger perspective. In a large population-based cohort of 46,177 older adults with type 2 DM, initiation of GLP-1RA therapy was associated with an 11% increased risk of fragility fractures compared with DPP-4 inhibitors or SGLT2 inhibitors.[15] Notably, GLP-1 therapy was also associated with lower all-cause mortality. However, mortality was not reported in association with or without fragility fractures.

Table 1. Evolution of evidence on GLP-1RA and skeletal effects.

Study	Year	Study design	Population	Drug/exposure	N.	Reported follow-up	Primary/major outcome	Skeletal/body-composition outcome	Key finding
Lipscombe *et al.*[5]	2007	Retrospective cohort	Adults ≥66 y with diabetes *vs* matched controls	Diabetes status	197,412 diabetes; 401,400 controls	Mean 6.1 y	Hip fracture	Incident hip fracture	Diabetes was associated with increased hip fracture risk
Leslie *et al.*[6]	2013	Retrospective cohort	Women ≥50 y undergoing DXA; 2356 with diabetes	Diabetes status	29,407 total	Mean 4.7 y	Major osteoporotic fracture	Lumbar spine TBS; fracture risk	Diabetes was associated with lower TBS despite higher BMD; TBS captures fracture risk independent of BMD
Su *et al.*[8]	2015	Meta-analysis of randomized controlled trials	T2DM patients in GLP-1RA RCTs	Liraglutide or exenatide	16 RCTs; 11,206 patients	Variable across trials	Fracture incidence	Bone fracture events	Divergent conclusions between GLP-1RA drugs; liraglutide associated with reduced fractures while exenatide associated with increased fractures
Driessen *et al.*[9]	2015	Retrospective cohort	Adults with T2DM initiating antidiabetic therapy	GLP-1RA *vs* other antihyperglycemic drugs	216,816 total; 3,392 GLP-1RA users	Mean 2.0 y	Incident fracture	Any fracture	No statistically significant association between GLP-1RA use and fracture risk
Yeung *et al.*[10]	2019	Systematic review and meta-analysis	Older adults	Sarcopenia status	52,838 individuals across 36 studies	Variable across studies	Falls/fractures	Falls and fractures	Sarcopenia was associated with increased fractures and falls
STEP 1[1]	2021	Randomized, double-blind, placebo-controlled phase 3 trial (DXA substudy)	Adults with overweight/obesity without diabetes	Semaglutide 2.4 mg *vs* placebo	1961 overall; 140 in DXA substudy	68 weeks	Weight loss	Fat mass, lean mass, visceral fat by DXA	In the DXA subgroup, semaglutide reduced fat mass more than lean mass; both types of mass decreased
STEP 2[12]	2021	Randomized, double-blind, placebo-controlled phase 3 trial	Adults with T2DM and overweight/obesity	Semaglutide 2.4 mg or 1.0 mg *vs* placebo	1210	68 weeks	Weight loss	No prespecified skeletal endpoint	Semaglutide reduced body weight compared to placebo
STEP 3[13]	2021	Randomized, double-blind, placebo-controlled phase 3 trial	Adults with overweight/obesity	Semaglutide 2.4 mg *vs* placebo with lifestyle intervention	611	68 weeks	Weight loss	No prespecified skeletal endpoint	Semaglutide plus behavioral therapy reduced weight more than placebo plus behavioral therapy
STEP 4[14]	2021	Randomized, double-blind withdrawal phase 3 trial	Adults with overweight/obesity after semaglutide run-in	Continued semaglutide *vs* placebo	803 randomized	68 weeks total	Weight maintenance	No prespecified skeletal endpoint	Semaglutide discontinuation led to weight regain
Al-Mashhadi *et al.*[24]	2022	Propensity-matched cohort	T2DM treated with metformin plus GLP-1RA or DPP-4i	GLP-1RA *vs* DPP-4i	42,816 identified; 32,266 matched	Median follow-up: 642 days (GLP-1RA) *vs* 529 days (DPP-4i)	Major osteoporotic fracture	Hip, vertebral, humerus, forearm fractures	No significant difference in fracture risk between GLP-1RA and DPP-4i
Jensen *et al.*[17]	2024	Secondary analysis of randomized clinical trial	Adults with obesity after diet-induced weight loss	Exercise, liraglutide, combination, or placebo	195	1-year intervention	Bone health after weight loss	Hip, spine, forearm BMD	Liraglutide alone reduced BMD; exercise mitigated bone loss
Hansen *et al.*[25]	2024	Randomized, double-blind, placebo-controlled phase 2 trial	Adults with increased fracture risk	Once-weekly semaglutide *vs* placebo	64	52 weeks	Bone formation marker (P-PINP)	BMD, bone turnover markers	No increase in bone formation based on P-PINP; increased bone resorption observed
BELIEVE (Heymsfield *et al.*)[20]	2026	Randomized, double-blind, placebo-controlled phase 2 trial with extension	Adults with obesity combination, or placebo	Bimagrumab, semaglutide,	507	48-week primary; extension to 72 weeks	Body weight change	Fat mass, lean mass, visceral adipose tissue	Combination therapy reduced fat mass while attenuating lean mass loss compared with semaglutide alone
Kasher Meron *et al.*[15]	2026	Retrospective cohort	Adults ≥65 y with T2DM	GLP-1RA *vs* DPP-4i/SGLT2i	46,177 (11,257 GLP-1RA; 34,920 comparators)	Median 34.7 months	First fragility fracture	Major fragility fractures	GLP-1RA initiation associated with increased fracture risk and reduced all-cause mortality

GLP-1RA, glucagon-like peptide-1 receptor agonist; T2DM, type 2 diabetes mellitus; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; RCT, randomized controlled trial; TBS, Trabecular Bone Score; y, years.

The significance of this recent study and its observed association is closely tied to the expanding modern use of these agents.[4,15] With a growing population of adults with type 2 DM, increasing implementation efforts globally,[16] and as evidence increasingly supports cardiometabolic benefits and weight-loss effects of GLP-1RAs, it is essential to specifically assess and better define the skeletal implications for this population at high-risk for fracture.[1-6] The Meron *et al.* study should not diminish enthusiasm for GLP-1RA therapies in this population but broaden our understanding of the safety and outcomes of their use.

Several mechanisms may explain the observed association between GLP-1RA therapy and fragility fractures. An indirect mechanism, GLP-1 induced weight loss reduces mechanical loading on bone, which may promote bone resorption in susceptible patients. Reduced caloric intake, frequent with GLP-1RA use, may lead to decreased protein and calcium consumption, both essential for bone health.[4] Additionally, GLP-1RA associated weight loss is not completely selective for adipose-tissue, in which some weight loss is skeletal muscle mass and may contribute to increasing fall risk and potentially fracture susceptibility.[10]

Clinical studies have reported changes in bone density and bone turnover markers that were associated with GLP-1RA therapy.[17] Conversely, GLP-1 signaling may also have direct effects on bone cells. The net clinical effect therefore may be a balance of competing mechanisms, with indirect effects related to weight loss, nutrition, muscle loss, and falls being a predominating concern in at-risk older populations.

A critical limitation of current obesity pharmacotherapy is that medication-induced weight loss with GLP-1RA therapy includes more than adipose-tissue alone. A substantial proportion of weight may be lean mass, which can lead to functional limitations.[10,11] While reductions in lean mass may account for more than just contractile skeletal muscle, recent literature has emphasized the importance of evaluating muscle function and body composition in addition to pure weight change. Nevertheless, loss of muscle or bone mass may be particularly clinically relevant in populations where sarcopenia, frailty, and fracture risk are already increased.[18,19]

In older adults, this loss of skeletal muscle may exacerbate sarcopenia and increase fracture risk.[10] Clinical trials are underway to address this limitation.[20] If therapies, such as combination pharmacotherapy, can more selectively reduce adipose mass compared to lean mass, then it may be shown one day to have preferable outcomes for patients at increased skeletal event risk. Previous work with an anabolic-catabolic transfer agent, s-pindolol, has shown favorable lean mass effects in those with cancer cachexia, and this is being translated into ongoing work in the context of GLP-1RAs with the upcoming PROACT 1 and PROACT 2 trials.[21,22] These findings and ongoing work are a testament to optimizing body composition.

For clinicians, these findings have practical implications. While GLP-1RAs provide substantial benefit in regard to glycemic control, obesity, and cardiovascular events, there must be a balance for older or frail patients. Strategies must include nutritional optimization, resistance exercise,[10] consideration of bone density surveillance, and individualized risk-benefits assessments. Recent expert consensus further emphasizes monitoring of nutritional status, body weight, and body composition during GLP-1RA therapy, with consideration of intervention when appropriate.[23]

Future research should address the relationship of GLP-1RA drugs, fracture occurrence, and post-fracture outcomes. While fragility fractures in older adults are associated with increased morbidity and mortality, it is unknown if fractures in those on GLP-1RAs have different outcomes, particularly in light of the Meron *et al.* finding of increased fragility fracture risk alongside an all-cause mortality benefit in those on GLP-1RA.

GLP-1RAs provide substantial glycemic and other metabolic benefits, but their expanding use may introduce unintended risk, particularly in older adults with DM. These findings represent the shift in their use and focus should be given for an integrated approach to their use. The goal is not to restrict their use, but to ensure GLP-1RA benefits are achieved without overlooking skeletal vulnerability and other unintended consequences.

Ethics approval and consent to participate

Not required.

Conflict of interest

JDA has no conflicts of interest to declare. AJSC declares consulting fees from Bayer, Boehringer Ingelheim, Eli Lilly, GSK, Servier, Vifor, Actimed, Cardiac Dimensions, Corvia, ESN Cleer, Faraday, Impulse Dynamics, Respicardia; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, GSK, Novartis, Novo Nordisk, Vifor, Viatris; participation on a Data Safety Monitoring Board or Advisory Board for Impulse Dynamics. SDA declares Grants from CSL-Vifor and Abbott Laboratories, and personal fees for consultancies, trial committee work and/or lectures from Actimed, Alleviant, Amgen, Astra Zeneca, Bayer, Berlin Heals, Bimyo, Boehringer Ingelheim, Brahms, Cardiac Dimensions, Cardior, Cordio, Corvia, CVRx, Cytokinetics, Edwards, Impulse Dynamics, Lilly, Mankind Pharma, Novo Nordisk, Occlutech, Pfizer, Pulnovo, Regeneron, Relaxera, Repairon, Scirent, Sensible Medical, Veru, Viscardia, Vivus, and V-Wave/JNJ. Named co-inventor of two patent applications regarding MR-proANP (DE 102007010834 & DE 102007022367), but he does not benefit personally from the related issued patents.

Authors' contributions

All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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