Semaglutide: Beyond weight loss, what's the real reason it works?

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> Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have reshaped the management of obesity and type 2 diabetes, offering substantial weight reduction and glycemic control. But the clinical utility of this class, particularly semaglutide, appears to extend beyond its established metabolic benefits, prompting a closer look at its broader therapeutic potential. The question for clinicians is not just how well these drugs work for their primary indications, but where else they might prove useful.

KEY TAKEAWAYS

- The Pivot: GLP-1 RAs, including semaglutide, are under investigation for applications in orthopedics, specifically bone metabolism, cartilage preservation, and surgical outcomes.
- The Data: Scoping reviews highlight emerging, though not yet definitive, evidence for GLP-1 RAs in orthopedic care, suggesting beneficial effects on bone health and cartilage.
- The Action: Clinicians should monitor ongoing research into GLP-1 RA effects on musculoskeletal health and cardiovascular outcomes beyond diabetes, recognizing these are currently investigational areas.

Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), has fundamentally altered the therapeutic market for patients with obesity and type 2 diabetes. Its mechanism of action involves mimicking the endogenous GLP-1 hormone, leading to glucose-dependent insulin secretion, suppression of glucagon secretion, delayed gastric emptying, and a reduction in appetite through central nervous system effects. This action drives its efficacy in weight management and glycemic control, making it a cornerstone therapy for millions.3

The drug's success in its primary indications has naturally spurred interest in its potential for other conditions, particularly those often comorbid with obesity or type 2 diabetes. Researchers are now exploring whether the pleiotropic effects of GLP-1 RAs extend to areas like cardiovascular health, beyond the direct benefits of weight and glucose reduction, and even into musculoskeletal domains. This expansion of inquiry reflects a growing understanding that metabolic dysfunction impacts nearly every organ system, and interventions targeting core metabolic pathways may yield systemic benefits.

Beyond Metabolic Control: Orthopedic Implications

The role of GLP-1 RAs in orthopedic care is an emerging area of investigation, with several reviews attempting to synthesize the nascent evidence. Regmi, Niraula, and Sami conducted a scoping review in 2026, published in the Indian Journal of Orthopaedics, specifically assessing the potential applications of GLP-1 RAs in orthopedics.1 Their work highlighted beneficial effects on bone metabolism, cartilage preservation, and surgical outcomes, areas traditionally

managed with distinct pharmacological or surgical interventions.

The review by Regmi and colleagues noted that while GLP-1 RAs are extensively used for obesity and type 2 diabetes, their broader applications in orthopedics stem from observed effects on bone health. Obesity itself is a risk factor for various orthopedic complications, including osteoarthritis, fractures, and poorer surgical outcomes. If GLP-1 RAs can mitigate some of these risks, either directly or indirectly through weight loss, their value proposition expands considerably. The authors specifically looked at how these agents might influence bone mineral density, bone turnover markers, and the structural integrity of cartilage.

The precise mechanisms by which GLP-1 RAs might exert orthopedic benefits are still under elucidation. One hypothesis centers on the direct effects of GLP-1 receptors found on osteoblasts and osteoclasts, suggesting a potential for direct modulation of bone remodeling. Another pathway involves the anti-inflammatory properties of GLP-1 RAs, which could reduce systemic inflammation contributing to cartilage degradation and bone loss. Reduced inflammation could be particularly relevant in conditions like osteoarthritis, where chronic low-grade inflammation plays a significant role in disease progression. The weight loss induced by semaglutide also reduces mechanical stress on joints, which is a straightforward, but often overlooked, orthopedic benefit.

Still, the evidence base for direct orthopedic benefits remains largely preclinical or observational. The scoping review synthesized existing data, but it did not present new randomized controlled trials powered for orthopedic endpoints. Clinicians should interpret these findings as hypothesis-generating, indicating areas for future rigorous investigation rather than immediate changes in orthopedic practice. The review did not quantify specific improvements in bone mineral density or reductions in fracture risk with specific GLP-1 RAs, nor did it provide data on cartilage volume preservation or improvements in arthroplasty outcomes with statistical precision. These are critical gaps that future research must address.

Cardiovascular Reach: Heart Failure with Preserved Ejection Fraction

Beyond orthopedics, the cardiovascular benefits of GLP-1 RAs are also under scrutiny, particularly in heart failure with preserved ejection fraction (HFpEF). Parizad, Hatwal, and Taban Sadeghi published a systematic review in Vascular Health and Risk Management in 2026, detailing clinical advances in HFpEF and exploring therapeutic and mechanistic evidence.2 Their review, while broad, specifically mentioned GLP-1 RAs as agents with emerging applications due to their beneficial effects on various systemic parameters.

HFpEF represents a significant clinical challenge, characterized by high morbidity and mortality, with limited effective treatments until recently. Many patients with HFpEF also have obesity, type 2 diabetes, and hypertension, creating a complex web of comorbidities. The systematic review highlighted that GLP-1 RAs, through their effects on weight loss, glycemic control, and potentially direct cardiac mechanisms, could offer a therapeutic avenue. The reduction in body weight itself can alleviate cardiac workload and improve diastolic function, which is often impaired in HFpEF. For a deeper understanding of how obesity management impacts cardiovascular health, clinicians might refer to our previous coverage on bariatric surgery and emerging pharmacotherapies.

The mechanisms linking GLP-1 RAs to improved HFpEF outcomes are likely multifactorial. Beyond weight and glucose reduction, GLP-1 RAs have shown effects on blood pressure, endothelial function, and inflammation, all of which contribute to the pathophysiology of HFpEF. Some preclinical studies suggest direct myocardial effects, including improved myocardial energetics and reduced fibrosis, though these findings require robust clinical validation. The review

by Parizad and colleagues synthesized existing evidence, pointing towards a potential for GLP-1 RAs to improve clinical outcomes in HFpEF patients, particularly those with comorbid obesity and diabetes.

But the systematic review did not provide specific trial data for semaglutide or other GLP-1 RAs in HFpEF, nor did it quantify reductions in hospitalizations or improvements in quality of life with statistical precision. The evidence remains at an early stage, primarily observational or derived from subgroup analyses of trials focused on other cardiovascular endpoints. Dedicated, large-scale randomized controlled trials specifically designed to assess GLP-1 RAs in HFpEF are necessary to establish definitive efficacy and safety profiles in this patient population. Until then, clinicians should consider these as potential, not established, benefits.

The Broader Context: Diabesity and Polypharmacy

The expansion of GLP-1 RA applications is inextricably linked to the growing global burden of 'diabesity', a term reflecting the intertwined epidemics of type 2 diabetes and obesity. Galasso, Caporusso, and Volatile addressed this in their 2026 review in Current Obesity Reports, focusing on the pharmacological management of diabesity and emerging therapies.3 Their review reiterated the extensive utilization of GLP-1 RAs in treating both conditions, setting the stage for exploring their wider systemic effects.

The review emphasized that GLP-1 RAs are not merely glucose-lowering or weight-reducing agents; they are systemic metabolic modulators. This broader understanding drives the investigation into their effects on other organ systems. The authors highlighted that the beneficial effects on bone metabolism, cartilage preservation, and surgical outcomes, as seen in the orthopedic context, are likely downstream consequences of improved metabolic health and reduced systemic inflammation. This holistic view of GLP-1 RAs positions them as agents with potential to address multiple comorbidities simultaneously, a critical consideration in managing complex patients.

The challenge, however, lies in translating these observed or hypothesized benefits into actionable clinical guidance. While the concept of a single agent addressing multiple aspects of diabesity and its complications is appealing, each new application requires rigorous, dedicated clinical trials. The review by Galasso and colleagues provided a comprehensive overview of current and emerging therapies for diabesity, but it did not offer new data on specific orthopedic or cardiovascular endpoints. It served more as a conceptual framework for understanding why these broader applications are being explored.

One practical consideration for clinicians is the increasing polypharmacy often seen in patients with diabesity and its complications. If a single agent like semaglutide can address multiple aspects of a patient's health, it could potentially simplify medication regimens and improve adherence. But the cost-effectiveness and long-term safety of such broad applications need careful evaluation. For clinicians managing complex endocrine and metabolic conditions, the Oxford Handbook of Endocrinology and Diabetes offers a practical reference for navigating these evolving treatment guidelines.

The Evidence Gap: What We Don't Yet Know

Despite the enthusiasm surrounding the expanded potential of semaglutide and other GLP-1 RAs, significant evidence gaps remain. The scoping and systematic reviews cited here, while valuable for synthesizing existing literature, primarily highlight areas of emerging interest rather than definitive clinical proof. For instance, the orthopedic benefits, such as improved bone metabolism or cartilage preservation, are largely inferred from preclinical models or small observational studies. There are no large, randomized, placebo-controlled trials specifically designed to assess fracture rates or

progression of osteoarthritis in patients treated with semaglutide.

Similarly, while GLP-1 RAs show promise in HFpEF, the systematic review did not present conclusive evidence from dedicated trials. The cardiovascular benefits established for GLP-1 RAs, such as reductions in major adverse cardiovascular events (MACE) in patients with type 2 diabetes and established cardiovascular disease, are distinct from direct improvements in HFpEF outcomes. These MACE benefits are often driven by reductions in atherosclerotic events, which may not directly translate to improvements in the unique pathophysiology of HFpEF. Clinicians must differentiate between these established benefits and the still-investigational applications.

The open-label nature of some early studies and the reliance on surrogate endpoints are obvious caveats. Many of the observed 'benefits' in these emerging areas might be secondary to weight loss or improved glycemic control, rather than direct, independent effects of GLP-1 receptor agonism on bone or cardiac tissue. Disentangling these direct versus indirect effects requires sophisticated trial designs and mechanistic studies. The duration of follow-up in many studies also falls short of what is needed to assess long-term outcomes like fracture prevention or sustained improvements in heart failure symptoms. For example, a 24-week study might show changes in bone turnover markers, but it cannot predict a reduction in fractures over several years.

The patient populations studied in the primary GLP-1 RA trials were often specific, typically individuals with type 2 diabetes and/or obesity. Whether the observed benefits extend to patients without these primary indications, but with, for example, isolated osteoarthritis or HFpEF without diabetes, remains unclear. This specificity matters for generalizability. The cost of these therapies also presents a barrier, and demonstrating broad, independent benefits across multiple organ systems would be important for expanding access and justifying their use in new indications. The current evidence does not yet support routine prescribing of semaglutide for primary orthopedic or HFpEF indications outside of its established roles in obesity and diabetes.

Looking Ahead: The Next Wave of Evidence

The ongoing research into GLP-1 RAs suggests a future where these agents may play a much broader role in chronic disease management. The initial success in obesity and diabetes has opened doors to exploring their potential in a range of conditions where metabolic dysfunction is a contributing factor. This includes not only the orthopedic and cardiovascular applications discussed but potentially other areas like neurodegeneration and renal disease, where early signals have also emerged. The scientific community is actively pursuing these avenues, with numerous trials underway.

The next wave of evidence will need to come from large, well-designed, randomized controlled trials powered to detect differences in hard clinical endpoints relevant to these new indications. For orthopedics, this means trials assessing fracture incidence, rates of joint replacement, or objective measures of cartilage health. For HFpEF, it means trials focused on heart failure hospitalizations, cardiovascular mortality, and improvements in functional capacity. These studies will provide the definitive answers clinicians need to confidently expand the use of semaglutide and similar agents.

Until then, clinicians should remain informed but cautious. The current data, while intriguing, are not yet sufficient to warrant off-label prescribing for primary orthopedic or HFpEF indications. The focus should remain on optimizing GLP-1 RA use for their approved indications, leveraging their established benefits in weight management and glycemic control, and observing for any incidental improvements in comorbid conditions. The field is dynamic, and what is investigational today may become standard practice tomorrow, but only with robust evidence. The paradox of GLP-1s,

where weight loss is achieved but physical activity may decline, as discussed in our recent article, also highlights the complexity of these systemic effects.

CLINICAL IMPLICATIONS

The expanding narrative around semaglutide and other GLP-1 RAs is compelling, but clinicians must resist the urge to extrapolate beyond the data. While the idea of a single agent addressing multiple comorbidities is attractive, the evidence for direct orthopedic or HFpEF benefits, independent of weight loss and glycemic control, remains largely speculative. These are not yet established indications, and prescribing based on scoping reviews is premature.

For now, the primary utility of semaglutide remains firmly in obesity and type 2 diabetes. Any observed improvements in musculoskeletal health or heart failure symptoms in these patients should be viewed as welcome secondary effects, not primary treatment goals. The industry, particularly Novo Nordisk, will undoubtedly pursue these new indications, but the bar for regulatory approval and widespread clinical adoption is high, requiring dedicated, large-scale trials.

Patients, often exposed to enthusiastic media coverage, may inquire about these broader benefits. Clinicians must manage expectations, explaining that while research is ongoing, current evidence does not support using semaglutide as a primary treatment for conditions like osteoarthritis or HFpEF without co-existing obesity or diabetes. The focus should remain on evidence-based care within approved indications, while keeping an eye on future developments.

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