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Tirzepatide and Dual Incretin Agonism in Musculoskeletal Medicine: Metabolic Effects, Regenerative Potential, and Clinical Implications: A Current Concept Review

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ABSTRACT

Background: Potent incretin-based therapies, particularly tirzepatide, can induce significant and sustained reductions in body weight and fat mass alongside broad cardiometabolic improvements, thereby forging a new link between metabolic and musculoskeletal medicine. This study reviews the studies on tirzepatide and dual incretin agonism in musculoskeletal medicine

Methods: This current concept review provides a focused conceptual synthesis of studies on tirzepatide, dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 (GIP/GLP-1) agonists, obesity, osteoarthritis (OA), cartilage biology, body composition, skeletal muscle, skeletal health, arthroplasty, perioperative management, and regenerative orthopedics. Particular emphasis is placed on randomized clinical trials (RCTs), systematic reviews, meta-analyses, and translational studies available up to September 2026. Finally, we presented a framework termed "metabolic optimization of the regenerative host." This framework entails identifying and modifying systemic metabolic factors that may influence the environment surrounding joint preservation, arthroplasty, rehabilitation, tissue repair, and regenerative interventions.

Results: The orthopedic significance of these therapies cannot be inferred solely from weight loss. Evidence from RCTs supports symptomatic improvement with incretin-based obesity treatment in obesity-related knee OA; however, the strongest trial evidence regarding joint outcomes currently pertains specifically to semaglutide, not tirzepatide. Studies on tirzepatide have demonstrated substantial changes in fat mass, lean mass, and muscle composition, while emerging observations raise unresolved questions regarding skeletal health. Evidence concerning

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arthroplasty remains largely retrospective and heterogeneous, and preclinical signals of cartilage protection do not, in themselves, prove structural modification or human cartilage regeneration.

Conclusion: Tirzepatide is a relevant clinical model for profoundly altering host characteristics, rather than as a regenerative drug in its own right. The proposed framework is hypothesis-generating in nature and requires validation through prospective studies incorporating structural imaging, assessments of body composition and muscle function, skeletal health monitoring, metabolic and inflammatory biomarkers, and intervention-specific outcomes.

Keywords: Tirzepatide, GIP, GLP-1, Obesity, Osteoarthritis (OA), Cartilage, Skeletal muscle, Bone, Arthroplasty, Regenerative medicine, Metabolic prehabilitation, Host optimization

Highlights

- Obesity affects musculoskeletal health through mechanical and metabolic pathways.
- Tirzepatide substantially modifies body weight, adiposity, and metabolic status; direct musculoskeletal tissue regeneration remains unproven..
- Muscle and bone function should be assessed alongside weight loss in patients with knee OA.
- Knee OA benefits from incretin therapy are supported mainly by RCTs of semaglutide.
- Metabolic host optimization is a testable framework for orthopedic surgery and regenerative care.

Plain Language Summary

Metabolic dysfunction, inflammation, abnormal fat distribution, reduced muscle quality, and changes in bone health may all influence osteoarthritis (OA), mobility, rehabilitation, surgery, and tissue repair. Tirzepatide, a dual GIP/GLP-1 receptor agonist, produces substantial weight loss, fat reduction, and metabolic improvement, but these effects should not be interpreted as direct regeneration of cartilage or other musculoskeletal tissues. Weight loss may also be accompanied by changes in lean mass, muscle composition, and potentially bone health. Clinical evidence suggests that incretin-based therapies can improve symptoms in obesity-related knee OA, although the strongest evidence currently comes from RCTs of semaglutide rather than tirzepatide. This article proposed a host metabolic optimization approach that considers metabolic health, muscle function, nutrition, skeletal integrity, and physical capacity together. This concept is promising but remains a hypothesis and requires prospective clinical validation.

Introduction

In orthopedics, obesity has traditionally been viewed as a mechanical risk factor. This view is incomplete. Adipose tissue is metabolically and immunologically active, and obesity is associated with insulin resistance, altered adipokine signaling, ectopic fat accumulation, and chronic low-grade systemic inflammation [1-3]. In osteoarthritis (OA), these abnormalities interact with mechanical loading, affecting cartilage, synovium, subchondral bone, peri-articular muscles, and pain pathways. Recent studies on metabolic and cardiometabolic OA further support the view that—at least in some patients—systemic metabolic abnormalities may modify disease rather than merely accompany excess weight [4]. Consequently, we are dealing with a whole-joint disorder where body weight is significant but does not fully capture the patient's biological status. This distinction is crucial because musculoskeletal treatments do not operate in a vacuum. Joint-preserving procedures, arthroplasty, rehabilitation, platelet-derived products, cell-based therapies, biomaterials, scaffolds, and tissue-engineered constructs are all applied to a host possessing a distinct metabolic, inflammatory, nutritional, muscular, vascular, and skeletal phenotype. Thus, a treatment may be technically identical between patients, but the biological environment in which it is expected to function differs significantly.

Although the musculoskeletal effects of incretin-based therapies and the evolving field of regenerative orthopedics have each been reviewed, their intersection remains insufficiently integrated within a systematic framework of metabolic optimization of the regenerative host. In this article, we used tirzepatide as the primary model, not because the direct evidence regarding musculoskeletal outcomes is stronger for it, but because dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 (GIP/GLP-1) agonists can induce substantial, measurable changes in body fat, glycemic status, ectopic fat, and body composition [5–8]. Thus, the key musculoskeletal question is not merely whether tirzepatide reduces body mass index (BMI). Rather, the question is whether this profound metabolic shift can alter the host in ways that are clinically significant regarding joint symptoms, structural disease, perioperative risk, functional reserve, tissue repair, or the response to regenerative interventions. This concept review explores this issue by distinguishing established evidence from potential—yet unproven—downstream effects.

Materials and Methods

This article provides a focused conceptual synthesis of studies on tirzepatide, dual GIP/GLP-1 agonists, obesity, OA, cartilage biology, body composition, skeletal muscle, skeletal health, arthroplasty, perioperative management, and regenerative orthopedics. Particular emphasis is placed on randomized clinical trials (RCTs), systematic reviews, meta-analyses, and translational studies available up to September 2026. This article is not a formal systematic review and does not generate a pooled effect estimate. Evidence is interpreted at three levels: Established clinical evidence (including the findings supported by RCTs or robust prospective human data), emerging or translational evidence (primarily encompassing human observational studies, secondary analyses, or converging clinical and preclinical findings), and conceptual or hypothesis-generating evidence (involving plausible biological propositions that lack sufficient direct clinical confirmation). These three levels constitute a narrative interpretive framework for this "current concept" study; the assessment is not a formal GRADE-based evaluation of certainty. Evidence from semaglutide or other GLP-1 receptor agonists is not automatically extrapolated to tirzepatide, given the latter's distinct dual GIP/GLP-1 pharmacology. Table 1 summarizes the evidence for incretin-based therapies across musculoskeletal domains.

Results

Obesity as an unfavorable musculoskeletal host

The term "metabolically unfavorable musculoskeletal host" stems from the observation that obesity operates through both biomechanical and systemic pathways. Increased body weight raises the load on weight-bearing joints. Concurrently, adipose tissue dysfunction contributes to insulin resistance, inflammatory signaling, altered adipokine profiles, and ectopic fat accumulation [1–3]. These processes may be associated with pain, synovial inflammation, cartilage degradation, subchondral

Table 1. Evidence for incretin-based therapies in musculoskeletal medicine

Domain	Principal Evidence	Is It Tirzepatide-Specific?	Current Interpretation
Weight reduction	Large phase 3 RCTs	Yes	Established
Metabolic improvement	Large RCTs	Yes	Established
Fat/lean mass	DXA substudy	Yes	Established body-composition change
Muscle composition	MRI analysis	Yes	Emerging; quality and quantity may diverge
Knee OA/function	RCT	No (semaglutide specific)	Strong class-related proof of concept
Chondroprotection	Mainly preclinical	Predominantly no	Translational / hypothesis-generating
Human cartilage regeneration	No adequate evidence	No	Unproven
Arthroplasty outcomes	Retrospective cohorts/ syntheses	Mainly class evidence	Promising associations; non-causal
BMD / fracture	Retrospective / emerging evidence	Partly	Uncertain; surveillance warranted
Enhanced regenerative response	No adequate clinical evidence	No	Conceptual

Abbreviations: BMD: Bone mineral density; DXA: Dual energy X-ray absorptiometry; MRI: Magnetic resonance imaging.

bone changes, and physical function, thereby supporting the concept of "metabolic OA phenotype" as opposed to a purely load-based OA model [4]. The most defensible interpretation of this framework is a phenotypic or endotypic hypothesis: it is unlikely that metabolic abnormalities play an equal role in all patients with OA.

For restorative and regenerative care, the host phenotype can be examined across interconnected domains: body fat, metabolic control, systemic inflammation, muscle quantity/quality, skeletal reserve, nutrition, and physical capacity. The value of this formulation lies not in implying that any single domain definitively dictates the success of all interventions, but rather in identifying measurable biological variables that may alter the environment in which tissue repair, rehabilitation, and regeneration occur. This hypothesis becomes useful only when these variables are linked to meaningful clinical outcomes in prospective studies.

Tirzepatide as a model of metabolic host modification

Beyond its established metabolic and weight-reducing effects, tirzepatide can provide an accessible clinical model of profound, measurable host modification. Dual GIP/GLP-1 receptor agonism can alter body weight, total and visceral fat, glycemic status, ectopic fat, and body composition over a clinically meaningful timeframe [5–8]. These upstream changes create a translational opportunity to ask whether biological changes alter the systemic milieu in which musculoskeletal disease, rehabilitation, surgery, and tissue repair occur. However, these changes do not, in themselves, demonstrate a direct effect on joint or connective tissues.

Thus, from an orthopedic perspective, the critical issue is the quality of the host transition, not merely the level of weight loss. Reductions in deleterious fat and mechanical load may coincide with losses in lean mass, alterations in muscle composition, or uncertainties regarding bone health. Ideally, a favorable clinical trajectory should reduce metabolic and mechanical risk while preserving functional reserve and skeletal integrity. Subsequent sections examine tirzepatide along the integrated fat-muscle-bone axis, treating its established systemic effects as upstream exposures whose musculoskeletal consequences still require direct investigation.

Adiposity, metabolic control, and mechanical loading

Tirzepatide simultaneously activates GIP and GLP-1 receptors, resulting in significant body weight loss alongside broad metabolic improvements. In Jastreboff et al.'s study, mean weight loss at week 72 with tirzepatide doses of 5, 10, and 15 mg was 15%, 19.5%, and 20.9%, respectively, compared to 3.1% in the placebo group [5]. In their other study, long-term follow-up of participants with obesity and prediabetes showed that tirzepatide led to substantial weight loss through 176 weeks, and the progression to type 2 diabetes was significantly lower compared to the placebo [6]. These established systemic effects explain why tirzepatide serves as a model for altering host physiology; however, they should not be viewed as direct evidence of an orthopedic therapeutic effect. These effects are significant from a musculoskeletal perspective, as they can drive changes that go beyond the numerical weight reading on a scale. Decreased body mass/fat can reduce mechanical demands and alter the metabolic context for mobility, recovery, and rehabilitation. At the same time, BMI alone is an inadequate index; a patient may lose weight without necessarily becoming better prepared functionally, nutritionally, or skeletally for orthopedic treatment.

Muscle quantity/quality and functional reserve

A dual-energy X-ray absorptiometry (DXA) study demonstrated that, over 72 weeks, tirzepatide reduced body weight by 21.3%, fat mass by 33.9%, and lean mass by 10.9%; approximately three-quarters of the weight lost was fat mass, while one-quarter was lean mass [7]. These data should not be equated with inevitable pathological sarcopenia. Lean mass measured by DXA does not reflect contractile skeletal muscle mass, and some lean mass loss typically accompanies significant weight loss. Meta-analysis evidence on incretin therapies has also shown a concurrent reduction in both fat mass and lean mass, with the proportion of weight loss attributed to lean mass generally overlapping with that observed in intensive lifestyle interventions [9, 10].

Magnetic resonance imaging (MRI) data have provided important contradictory results. In an MRI study, tirzepatide-associated weight loss was accompanied by reduced hip muscle volume, but intramuscular fat infiltration simultaneously decreased [8]. Thus, muscle quantity and quality may change. In orthopedic patients—particularly the elderly, those with OA, frailty, or sarcopenic obesity, or those facing reconstructive surgery—functional reserve may provide more informative

data than lean mass alone. A recent review study indicated that resistance training can reduce the proportion of weight loss attributed to lean mass. However, this has not yet been established as a specific orthopedic strategy for tirzepatide [10]. Future studies should integrate body composition assessment with quadriceps strength, gait speed, the chair-stand test, physical activity, and patient-reported function.

Skeletal health

Skeletal health offers another reason to avoid a strictly weight-centric interpretation. Improvements in metabolic health may be biologically beneficial for bone, whereas substantial weight loss reduces mechanical loading and may be associated with a loss of bone mass. A 2026 retrospective DXA study comparing users of semaglutide/tirzepatide with a matched control group observed a decrease in bone mineral density (BMD) at the total hip and femoral neck in both groups; among participants without diabetes, the annual decline in total hip BMD was greater in those receiving GLP-1 receptor agonists [11]. A real-world cohort study also linked the initiation of tirzepatide use with a higher risk of osteoporosis or fragility fractures, compared to other GLP-1 receptor agonists [12]. In contrast, a meta-analysis of RCTs on anti-obesity strategies did not show a significant overall reduction in BMD associated with pharmacological interventions, suggesting that skeletal effects may vary by intervention, population, and weight-loss level [13]. Neither of these two observational studies focused on tirzepatide established a causal relationship, nor was the broader body of randomized evidence sufficiently specific to rule out clinically significant risk in vulnerable subgroups [12, 13]. Residual confounders, baseline skeletal risk, diabetes status, the level and rate of weight loss, the intensity of monitoring, nutrition, muscle function, and falls can all influence the observed outcomes. Therefore, tirzepatide is neither harmful to skeletal health, nor can it be assumed to have absolutely no effect on skeletal health in all patients. In high-risk patients, metabolic optimization should include attention to skeletal health, rather than focusing solely on weight loss.

Joint preservation: From symptom improvement to structural outcomes

The most compelling immediate musculoskeletal rationale for potent anti-obesity therapy is the reduction of mechanical load along with improved mobility and rehabilitation capacity. RCTs on lifestyle interventions support weight loss and exercise as key clinical components of care for knee OA in the context of overweight or obesity. However, symptom improvement is not explained solely by the amount of weight lost. In an RCT, an 18-month community-based program combined with diet and exercise compared to an attention-control program resulted in greater significant weight loss and reduced knee pain measured by the Western Ontario and McMaster universities arthritis index (WOMAC) scale [14]. Another RCT provided the most direct, high-level evidence on incretin therapy: adults with obesity and moderate-to-severe knee OA who received semaglutide (2.4 mg) once a week experienced greater reductions in both body weight and knee pain than those receiving placebo [15]. While clinically significant, this finding requires careful interpretation. This study evaluated semaglutide rather than tirzepatide; thus, it establishes a class-level proof of concept for incretin therapy in obesity-related knee OA, rather than demonstrating specific analgesic or disease-modifying effects unique to tirzepatide.

The next evidence is related to structural disease modification. A 2025 systematic review identified seven preclinical studies and four human studies on the GLP-1 receptor agonists in OA. Preclinical findings suggested chondroprotective and immunomodulatory effects, including the potential inhibition of NF-κB-related pathways [16]. An observational study from the Shanghai osteoarthritis cohort involving patients with knee OA and type 2 diabetes linked the use of GLP-1 receptor agonists to a lower incidence of knee surgery, symptom improvement, and a slower rate of medial femorotibial cartilage loss [17]. Although this study is important, its observational design, specific metabolic population, and the potential for residual confounding preclude it from proving disease modification or a direct receptor-mediated effect on cartilage.

Accordingly, current evidence does not support characterizing tirzepatide—or the GLP-1 receptor agonists in general—as a cartilage-regenerating therapy. Symptom improvement, structural modification, and tissue regeneration are distinct concepts and should not be used interchangeably [15-17]. Questions specific to tirzepatide include: Can a greater mean weight loss be achieved through dual GIP/GLP-1 receptor agonists' translation into greater benefits for OA symptoms? Is symptomatic improvement accompanied by structural changes on quantitative imaging? Answering these questions requires conducting RCTs rather than extrapolation from other evidence.

Arthroplasty and the emergence of metabolic prehabilitation

Arthroplasty provides a suitable setting for testing the "host-centric" hypothesis, as obesity, diabetes, nutritional status, muscle function, and skeletal health can all influence perioperative risk and recovery. The rapid expansion of incretin therapies has created a natural overlap between metabolic medicine and joint reconstruction. However, most current evidence regarding arthroplasty—derived from retrospective studies—compares "drug exposure" with "drug non-exposure" rather than testing a predefined, prospective strategy for optimizing the surgical host [18–21]. This distinction sets metabolic prehabilitation apart from the simple goal of preoperative weight loss. A structured host-optimization process should define multidisciplinary targets for body fat, glycemic control, nutrition, muscle function, skeletal reserve, and physical capacity, and subsequently link the achievement of these goals to surgical and recovery outcomes. Incretin therapy, when used for an established metabolic indication, can be part of this pathway; however, current evidence does not support initiating tirzepatide solely to improve arthroplasty outcomes. Therefore, the following sections distinguish between observational signals in arthroplasty, the broader concept of prehabilitation, and perioperative pharmacological management.

Arthroplasty literature

Total joint arthroplasty is a treatment method where incretin therapy and orthopedic outcomes are rapidly converging. A 2026 systematic review comprising 15 retrospective cohorts and 318,143 patients reported potentially favorable associations between GLP-1 receptor agonist use and certain total hip arthroplasty/ total knee arthroplasty (THA/TKA) outcomes—specifically regarding periprosthetic joint infection (PJI) and readmission [18]. Another review of 15 retrospective arthroplasty studies reported favorable postoperative findings in 9 studies, mixed results in 3 studies, predominantly unfavorable outcomes in 2 studies, and no significant difference in one study. Overall, the evidence certainty was low [19]. A 2026 meta-analysis of 13 retrospective cohorts involving 1,408,609 THA/TKA patients demonstrated that exposure to GLP-1 receptor agonists was associated with reduced 90-day periprosthetic infection, fewer all-cause revisions, and lower readmission rates; however, an increased risk of periprosthetic fracture within one year—primarily following TKA—was also observed [20]. A systematic review also found no consistent, sustained medium-term benefit [21]. A recent orthopedic review also addressed GLP-1 receptor agonism in the context of obesity, OA, metabolic optimization, and arthroplasty complications [22].

While clinically significant, these data do not establish a causal relationship with medications. Treated and untreated patients may differ in terms of weight trajectory, diabetes severity, cardiometabolic control, healthcare delivery, socioeconomic status, treatment adherence, and other unmeasured factors. Furthermore, existing reviews regarding arthroplasty primarily evaluate medication exposure rather than a prospective, predefined intervention for host optimization [18–21]. Therefore, incretin therapy may eventually serve as a component of metabolic prehabilitation, rather than being a currently established strategy for preventing infection, revision, readmission, or fracture.

From conventional prehabilitation to metabolic prehabilitation

Conventional orthopedic prehabilitation emphasizes physical condition, smoking cessation, nutrition, and optimizing comorbidities. Evidence regarding prehabilitation prior to THA/TKA is heterogeneous. However, it supports potential short-term improvements in certain functional and postoperative outcomes, whereas evidence for preoperative weight-loss interventions remains based on a relatively limited number of RCTs [23, 24]. The incretin therapy era proposes a broader model—not a replacement for these established areas. The goal of metabolic prehabilitation is not merely to lower BMI, but to achieve a more favorable surgical host: reduced harmful body fat, adequate glycemic control, sufficient nutrition, preserved or improved muscle function, adequate skeletal reserves, enhanced physical capacity, and optimized cardiometabolic health. This formulation shifts the clinical endpoint but remains a proposed framework, not a validated perioperative pathway. If weight loss is accompanied by nutritional impairment, declining muscle function, or skeletal deterioration, a lighter weight does not necessarily make a patient a better surgical candidate. Conversely, changes in fat distribution, glycemic status, muscle quality, mobility, and inflammatory burden can be clinically significant, even if BMI alone does not reflect them. Existing literature on prehabilitation and preoperative weight loss supports multidimensional optimization [23, 24], but it has not yet shown that tirzepatide-based metabolic prehabilitation improves arthroplasty outcomes. Therefore, the emphasis should shift from weight-centric to host-centric optimization.

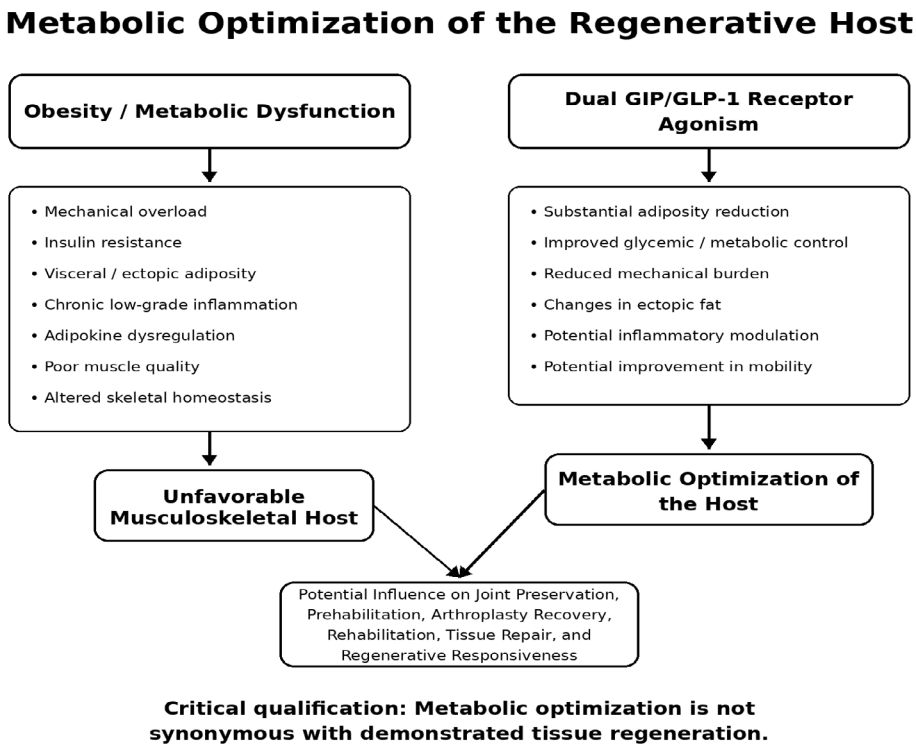


Figure 1. The conceptual model of metabolic optimization of the regenerative host

Perioperative medication management

Incretin-based therapies also raise specific perioperative considerations, as GLP-1 receptor agonists can delay gastric emptying, thereby increasing concerns about retained gastric contents and aspiration. Contemporary multi-society guidelines advocate for a personalized perioperative assessment rather than a uniform "stop or continue" rule for all patients [25]. The associated variables include gastrointestinal symptoms, the dose-escalation phase of therapy, dosage, aspiration risk, procedural characteristics, and the metabolic consequences of discontinuing treatment. Consequently, in orthopedic practice, coordination among the surgical, anesthesia, and prescribing teams is preferable to applying a single medication rule to all patients.

In the framework of host optimization, perioperative medication management should be integrated with the broader goals of metabolic prehabilitation rather than treated as an isolated decision regarding drug discontinuation. The optimal balance depends on the patient and the type of procedure; aspiration risk should be weighed against gastrointestinal tolerance, metabolic stability, nutritional status, and the consequences of stopping the medication. While current guidelines support personalized decision-making, prospective orthopedic data are still needed to determine how perioperative strategies influence surgical outcomes and recovery in patients receiving incretin therapy [25].

Regenerative orthopedics: From product-centric to host-centric approach

Regenerative orthopedics has traditionally focused on optimizing the "therapeutic product": Platelet-derived products, cell therapies, growth factor delivery systems, biomaterials, hydrogels, scaffolds, and tissue-engineered constructs. While this product-centric emphasis is logical, it may obscure a second source of variability: the recipient's biological status. A patient with limited visceral fat, good metabolic control, preserved muscle function, and a low systemic inflammatory burden may present a vastly different biological environment compared to a patient with insulin resistance, visceral obesity, chronic metabolic inflammation, sarcopenia, and poor physical reserve. This host-based perspective is also consistent with emerging regenerative literature emphasizing that therapeutic efficacy is shaped not only by the regenerative product itself but also by the biological microenvironment in which it operates.

Table 2. Proposed framework for metabolic optimization of the regenerative host

Domain	Suggested Measures	Why It Matters?
Adiposity	BMI, waist circumference, DXA fat mass, visceral adiposity	Separates total weight from harmful fat burden
Metabolic status	HbA1c, fasting glucose, insulin-resistance indices	Characterizes systemic metabolic state
Inflammation	hs-CRP and selected research cytokine panels	Tests inflammatory host modification
Muscle	DXA/MRI, quadriceps strength, gait speed, chair-rise	Distinguishes mass, quality, and functional reserve
Bone	DXA, fracture history, bone-turnover markers	Tracks skeletal trade-offs during major weight loss
Joint structure	Quantitative MRI; cartilage, synovial, subchondral outcomes	Separates symptomatic from structural effects
Clinical OA	WOMAC/KOOS, pain, activity, analgesic use	Captures patient-level benefit
Surgery	PJI, wound events, length of stay, readmission, revision surgery	Tests metabolic prehabilitation in arthroplasty
Regenerative response	Clinical, imaging, biomarker endpoints	Tests interaction between host optimization and intervention

Abbreviations: HbA1c: Hemoglobin A1C; DXA: Dual energy X-ray absorptiometry; MRI: Magnetic resonance imaging; hs-CRP: High sensitivity c-reactive protein; WOMAC: Western Ontario and McMaster universities arthritis index; KOOS: Knee injury and osteoarthritis outcome score; PJI: Periprosthetic joint infection

In bone regeneration, extracellular vesicle-based studies have shown the importance of coordinated osteogenic, angiogenic, and immunomodulatory signaling, while biomaterial studies have further demonstrated that macrophage phenotype and local immune regulation can substantially influence regenerative processes. Perioperative orthopedic data similarly suggest that the systemic inflammatory milieu is modifiable; for example, altered Interleukin-1/Interleukin-10 (IL-1/IL-10) profiles have been observed following allogeneic transfusion in patients undergoing THA [26-28]. Overall, these observations support the broader principle that regenerative and surgical outcomes emerge from an interaction between the intervention and the biological state of the host. This raises a distinct question: Can metabolic optimization improve the host environment in which musculoskeletal repair and regenerative interventions are expected to function? Currently, clinical evidence is insufficient to show that tirzepatide enhances the efficacy of platelet-rich plasma, cell therapy, cartilage repair techniques, biomaterial scaffolds, or other regenerative orthopedic interventions. Therefore, studies on weight loss, OA symptoms, or arthroplasty outcomes do not support improved regenerative efficacy. Tirzepatide should not currently be characterized as an adjunct for regenerative therapy.

The value of the host concept lies in its ability to transform speculation into a measurable research agenda. Patients undergoing a specific regenerative or joint-preserving intervention can be phenotyped regarding visceral fat, body composition, insulin resistance, systemic inflammation, muscle quality, skeletal health, and functional reserve. Changes in these variables during metabolic treatment can then be prospectively correlated with pain, function, quantitative imaging, biochemical markers, tissue-level outcomes, and response durability. In this model, regenerative medicine interconnects product biology, tissue biology, and host biology.

Metabolic optimization of the regenerative host

We propose a conceptual framework named "metabolic optimization of the regenerative host" (Figure 1, Table 2), which entails identifying and correcting systemic metabolic abnormalities that may influence musculoskeletal tissue homeostasis, repair, rehabilitation, or responses to orthopedic and regenerative therapies. This framework is intentionally conservative. Obesity and metabolic dysfunction can create an unfavorable host environment through interconnected metabolic, inflammatory, muscular, and skeletal pathways [1-4]. Tirzepatide can modulate several upstream variables by significantly reducing body weight and fat mass, improving glycemic and metabolic control, and inducing measurable changes in body composition and ectopic fat [5-8]. Reducing body mass also offers a logical pathway to alleviate mechanical loading on weight-bearing joints.

Downstream consequences remain less certain. Host modification could reasonably influence joint preservation, prehabilitation, post-arthroplasty recovery, rehabilitation, tissue repair, or regenerative responsiveness;

Table 3. Clinical and translational implications of incretin-based therapies in musculoskeletal medicine

Clinical Context	Potential Opportunity	Principal Concern	Priority Research
Obesity-related knee OA	Weight reduction, symptomatic improvement	Structural benefit unknown	Tirzepatide-specific OA RCT
Pre-THA/TKA obesity	Metabolic prehabilitation	Nutritional / lean-tissue compromise	Prospective host-optimization trials
Sarcopenic obesity	Reduced adiposity	Functional muscle loss	Strength and performance studies
High skeletal risk	Metabolic improvement	BMD / fracture uncertainty	Prospective bone surveillance
Regenerative orthopedics	Host optimization	No proven enhancement of regenerative response	Interaction trials
Rehabilitation	Reduced mechanical burden; improved mobility potential	Insufficient functional reserve	Functional outcome studies

Abbreviations: BMD: Bone mineral density; TKA: Total knee arthroplasty; THA: Total hip arthroplasty.

however, the latter two outcomes have not yet been demonstrated in humans. Therefore, this framework should be used to generate testable hypotheses rather than to imply a pre-established therapeutic effect. Table 3 summarizes the potential clinical opportunities, principal concerns, and priority research directions for incretin-based therapies in musculoskeletal medicine.

Boundaries of the framework

Using the conceptual framework depends on maintaining clear interpretive boundaries. Without these boundaries, a host-centric approach may be mistakenly interpreted as evidence that tirzepatide use is a regenerative therapy, or that all musculoskeletal observations regarding GLP-1 receptor agonists are directly generalizable to dual GIP/GLP-1 agonism. The aim of this framework is to prevent—not encourage—such conceptual overgeneralization. The boundaries also define what a successful future study should demonstrate. Symptom improvement should be distinguished from structural changes, and structural preservation from tissue regeneration. Also, proper host optimization should be assessed across domains such as body fat, metabolic control, muscle function, skeletal integrity, nutrition, and physical capacity, rather than only the weight loss level.

Three practical boundaries emerged for differentiation. First, metabolic optimization is not synonymous with tissue regeneration. Improvements in pain or function do not prove structural correction, nor does structural protection, in and of itself, indicate regeneration. Second, class-level effects should not be assumed to be specific to tirzepatide. Data on semaglutide and other GLP-1 receptor agonists may support biological plausibility or provide proof of concept at the class level. However, they cannot substitute for direct trials of the dual agonist. Third, weight loss is not the endpoint. The relevant musculoskeletal goal is to optimally balance body fat reduction, metabolic control, muscle function, skeletal integrity, nutrition, and physical capacity.

Research agenda: Turning the concept into a testable program

The next phase of research should move beyond retrospective associations and BMI-based endpoints. The RCT of tirzepatide in patients with knee OA should combine pain and functional assessments with structural imaging, as current RCTs are specific to semaglutide. Human structural signals also remain observational [15, 17]. Quantitative MRI (qMRI) should evaluate cartilage morphology and composition, synovitis, bone marrow lesions, and subchondral changes to determine whether symptomatic improvement is accompanied by structural modification. Body composition studies should include assessments of strength and function to interpret any loss of lean mass in the context of muscle quality and performance [9, 10]. Bone-related studies should also prospectively track DXA metrics, bone turnover markers, falls, fragility fractures, and periprosthetic fractures, while categorizing data by age, sex, diabetes status, baseline skeletal risk, and amount of weight loss [11-13].

In the context of arthroplasty, prospective studies should evaluate "structured metabolic prehabilitation" rather than merely drug exposure. Existing evidence suggests that prehabilitation and preoperative weight-loss interventions can influence certain outcomes; however, the literature is heterogeneous and fails to validate an optimal, incretin-specific pathway for host optimization [23, 24]. Future interventions should clearly define metabolic, nutritional, muscular, and skeletal targets and correlate them with infection rate, wound complications,

length of hospital stay, readmission rate, revision surgery, rehabilitation, and patient-reported outcomes. In regenerative orthopedics, interactive trials are needed: Patients undergoing a specific joint-preserving or regenerative intervention could be stratified or randomized based on structured metabolic optimization, with clinical outcomes, imaging data, biomarkers, body composition, and functional metrics collected in parallel.

Another priority is identifying phenotypes. OA should not automatically be assumed to be a uniform biological disease. Studies should determine whether insulin resistance, visceral fat, adipokines, systemic inflammation, muscle composition, or other metabolic variables can identify a subgroup that responds more favorably to metabolic intervention [4]. This is essential, as the average treatment effect within an unselected OA population might mask a clinically significant metabolic endotype. With the emergence of next-generation dual or multi-receptor agonists, comparative studies can determine whether differences in receptor pharmacology result in distinct musculoskeletal effects.

Discussion

The immediate takeaway from this current concept review is not that tirzepatide should be adopted in orthopedic practice as a musculoskeletal regenerative therapy, nor that it should currently be prescribed to modify OA structure or improve arthroplasty outcomes. A more defensible shift is conceptual: When potent metabolic therapy is employed in an orthopedic patient for an established metabolic indication, success should not be measured solely by amount of weight lost or reductions in BMI. It is more logical to characterize musculoskeletal benefit through the combined dynamics of body fat, metabolic control, symptoms, mobility, muscle function, nutritional status, and skeletal health.

This multidimensional perspective is particularly relevant for patients with obesity-related knee OA, sarcopenic obesity, high skeletal risk, or those scheduled for THA/TKA. In these scenarios, significant body fat reduction may be beneficial, yet the anticipated benefit should be weighed against potential declines in muscle function or skeletal vulnerability. The same logic applies to regenerative care: "host optimization" provides a research framework for enhancing the biological environment for treatment, rather than serving as a substitute for evidence demonstrating the actual efficacy of a specific regenerative product or procedure.

Conclusion

Tirzepatide and related incretin-based therapies have established a novel link between metabolic and musculoskeletal medicine. Tirzepatide has well-documented effects on body weight, body fat, and metabolic health. Broader evidence regarding incretins supports clinically meaningful symptomatic improvement in obesity-related knee OA and offers emerging but inconclusive signals concerning joint structure in humans and arthroplasty outcomes. While significant, the observational studies do not demonstrate the direct regeneration of human articular cartilage or other musculoskeletal tissues, nor do they indicate that tirzepatide enhances the efficacy of orthobiologics, cell-based therapies, cartilage repair techniques, or tissue engineering interventions.

A more defensible opportunity lies in shifting from a weight-centric model to a host-centric approach. The proposed framework of "metabolic optimization of the regenerative host" determines whether body fat, metabolic control, inflammation, muscle function, skeletal reserves, nutrition, and physical capacity can be improved purposefully before or alongside musculoskeletal treatment. This is clinically relevant, biologically plausible, and empirically testable, yet it remains a hypothesis. Its ultimate value depends on prospective evidence demonstrating that host modification alters patient-related structural, functional, surgical, or regenerative outcomes.

Ethical Considerations

Compliance with ethical guidelines

This article is a review study and did not involve human or animal samples.

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interpretation of the results, and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interests.

Statement on the use of AI tools

During the preparation of this Current Concept Review, ChatGPT (OpenAI), a generative artificial intelligence large language model, was used to assist with the preliminary drafting, organization, and English-language refinement of the Abstract, Introduction, and sections addressing tirzepatide, obesity-related musculoskeletal disorders, osteoarthritis, arthroplasty, regenerative orthopedics, metabolic host optimization, research priorities, and clinical conclusions. The tool also assisted in structuring evidence-summary tables and developing the conceptual framework presented in Figure 1. All AI-assisted material was critically reviewed and revised by the authors, who retain full responsibility for the scientific content, references, interpretations, conclusions, and integrity of the final manuscript.

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