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Tirzepatide in Sport: A Comprehensive Review of its Metabolic Impacts and Potential Applications for Athletes

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Abstract

Introduction

Tirzepatide, a dual agonist of glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, has emerged as a transformative metabolic therapy with exceptional efficacy in weight management and glycemic control. Its relevance in sports science is growing, with potential benefits in weight optimization, energy balance, and recovery. By influencing glucose homeostasis, fat oxidation, and systemic inflammation, tirzepatide may enhance athletic performance. This review examines its pharmacological effects, impact on body composition, and implications for endurance, strength, and recovery in athletes, while addressing ethical and regulatory considerations, including anti-doping concerns.

Purpose of the Work: To analyze tirzepatide's pharmacological actions, clinical effects, and potential applications in optimizing sports performance, recovery, and body composition.

Materials and Methods: A comprehensive review of scientific literature was conducted across databases including PubMed, Scopus, Web of Science, Embase, and Google Scholar. Search terms encompassed tirzepatide, GLP-1/GIP dual agonist, metabolic therapy, sports performance, body composition, endurance, and athlete recovery. Relevant studies were synthesized to compile findings.

Results: Tirzepatide provides significant metabolic benefits, such as enhanced fat oxidation, improved glucose regulation, and reduced systemic inflammation. Its effects on body composition include substantial fat mass reduction, particularly visceral adiposity, while preserving lean muscle mass. These attributes suggest its potential to enhance endurance via glycogen-sparing mechanisms and improve recovery after exercise. However, concerns about misuse in competitive sports underline the need for regulatory oversight. Further research is necessary to evaluate tirzepatide's long-term effects on athletic performance and address associated ethical challenges.

Keywords: Tirzepatide, GIP/GLP-1 dual agonist, metabolic therapy, sports performance, body composition, anti- doping, endurance, athlete recovery

Introduction

Tirzepatide is a first-in-class dual agonist that stimulates glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) receptors, offering synergistic benefits in glycemic control, appetite suppression, and energy expenditure. Initially developed for managing type 2 diabetes (T2D) and obesity, tirzepatide has demonstrated unprecedented clinical efficacy, with patients achieving weight losses of up to 22.5%—surpassing the effects of traditional GLP-1 receptor agonists like semaglutide [1,3,5].

In sports medicine, interest in tirzepatide has grown due to its potential to optimize body composition, enhance recovery, and improve performance. Metabolic flexibility, or the ability to switch efficiently between fat and carbohydrate utilization, is a critical determinant of athletic success, especially in endurance sports [7,8]. By promoting fat oxidation and improving insulin sensitivity, tirzepatide may enable athletes to achieve superior metabolic efficiency.

This review evaluates the pharmacological mechanisms, effects on body composition, implications for sports performance, and ethical considerations of tirzepatide use in competitive environments.

Pharmacodynamics and Mechanism of Action

Tirzepatide exerts its unique therapeutic effects through its dual agonism of GLP-1 and GIP receptors, targeting two distinct incretin pathways. This dual mechanism facilitates metabolic outcomes that surpass those achievable with monotherapy, positioning tirzepatide as a highly effective agent for addressing complex metabolic challenges such as obesity and type 2 diabetes [4,6].

GLP-1 Receptor Agonism

The glucagon-like peptide-1 (GLP-1) receptor pathway is central to tirzepatide's glucose-regulatory and weight- reducing effects. Activation of the GLP-1 receptor enhances glucose-stimulated insulin secretion in pancreatic β- cells while concurrently suppressing glucagon release in α-cells, thereby stabilizing blood glucose levels. This glucose-dependent mechanism minimizes the risk of hypoglycemia, a common concern in diabetes management [2,4].

Furthermore, GLP-1 receptor agonism delays gastric emptying, which slows the rate of nutrient absorption and mitigates postprandial glucose excursions. This delay also contributes to enhanced satiety and a reduction in caloric intake, as shown in trials where tirzepatide reduced hunger ratings more effectively than GLP-1 monotherapy [3,4,6].

Notably, GLP-1 receptor activation exerts significant effects on the central nervous system, particularly in the hypothalamus. Tirzepatide influences hypothalamic neural circuits by reducing activity in orexigenic pathways (e.g., neuropeptide Y and agouti-related peptide neurons) and enhancing anorexigenic signaling (e.g., pro- opiomelanocortin neurons). This modulation reduces hunger perception and promotes sustained satiety, contributing to the drug's profound impact on body weight and energy intake [7,11].

GIP Receptor Modulation

Glucose-dependent insulinotropic peptide (GIP) receptor activation represents a novel and complementary mechanism in tirzepatide's pharmacological profile. Unlike GLP-1, GIP influences both glucose metabolism and lipid utilization. Tirzepatide's agonism of the GIP receptor enhances insulin secretion in response to hyperglycemia, improving glucose disposal and peripheral insulin sensitivity [4,8].

In addition to its glucose-lowering effects, GIP receptor activation uniquely promotes fat oxidation and thermogenesis. Preclinical studies suggest that tirzepatide modulates adipose tissue metabolism by increasing lipolysis and reducing adipogenesis, leading to substantial reductions in fat mass. These effects are especially prominent in visceral adipose depots, which are closely associated with cardiometabolic risk [5,8].

Importantly, GIP receptor activity may also play a role in preserving lean muscle mass during weight loss. This feature is critical for athletes, where maintaining muscle strength and function is paramount to optimizing performance [5,7]. Tirzepatide's ability to promote fat-specific weight loss while sparing muscle tissue provides a distinct advantage over other weight-reduction therapies.

Anti-inflammatory Properties

Chronic low-grade inflammation is a hallmark of metabolic disorders and a significant factor influencing athletic recovery and performance. Elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), are associated with insulin resistance, impaired muscle repair, and increased oxidative stress[11,17]

Tirzepatide exhibits notable anti-inflammatory effects, reducing systemic markers of inflammation in clinical trials. By lowering IL-6 and TNF-α levels, tirzepatide enhances insulin sensitivity and mitigates the negative effects of oxidative stress on muscle tissue. This mechanism may be particularly beneficial for athletes undergoing intense training, as it facilitates faster recovery, reduces muscle soreness, and enhances overall metabolic health [3,11,17].

Hypothalamic Regulation of Energy Balance

The hypothalamus is a key regulator of energy homeostasis, integrating peripheral signals such as leptin, ghrelin, and insulin to maintain energy balance. Tirzepatide's central effects extend beyond appetite suppression to include modulation of hypothalamic pathways involved in energy expenditure.

By decreasing orexigenic signals (e.g., neuropeptide Y) and increasing anorexigenic pathways (e.g., melanocortin signaling), tirzepatide helps suppress excessive food intake and promote adherence to dietary regimens. This is particularly advantageous for athletes in weight-class sports or those aiming to optimize body composition without compromising performance [4,7].

Additionally, tirzepatide's hypothalamic actions may enhance metabolic efficiency by coordinating peripheral energy utilization with central appetite regulation. These effects further

amplify the drug's capacity to promote fat oxidation while preserving lean mass, making it a valuable tool for achieving and maintaining peak physical condition [4,7,8].

Effects on Body Composition and Weight Loss

Weight Loss Outcomes

Tirzepatide has demonstrated remarkable efficacy in achieving substantial weight reduction, surpassing the results of conventional therapies targeting obesity and type 2 diabetes. Clinical trials consistently report an average weight loss of 15–20% of initial body weight among participants, with some individuals achieving reductions as high as 22.5%. These unprecedented outcomes are driven by tirzepatide's multifaceted mechanisms of action, which include appetite suppression, enhanced fat oxidation, and increased energy expenditure [10,13,15].

Appetite suppression, mediated through GLP-1 receptor activation, reduces caloric intake by modulating hypothalamic pathways responsible for hunger and satiety. Simultaneously, GIP receptor activation promotes fat- specific energy utilization and thermogenesis, leading to improved overall metabolic efficiency. Such outcomes represent a significant advancement in weight-loss pharmacology, offering a powerful tool for athletes managing weight-sensitive goals in sports like wrestling, lightweight rowing, or mixed martial arts [11,15].

Fat Oxidation and Lean Mass Preservation

Unlike traditional caloric restriction, which often results in concurrent loss of muscle mass, tirzepatide selectively targets adipose tissue, thereby preserving or even enhancing lean mass. This property is of particular relevance in sports where body composition critically influences performance, such as cycling, bodybuilding, or combat sports. Clinical studies indicate that tirzepatide facilitates reductions in both subcutaneous and visceral adipose tissue, with visceral fat reductions being especially pronounced. The decrease in visceral fat not only improves aesthetic outcomes but also has profound implications for metabolic health, reducing markers of inflammation, enhancing cardiovascular function, and increasing endurance capacity [15,18].

Preservation of lean mass during weight loss is attributed to tirzepatide's ability to enhance insulin sensitivity and reduce systemic inflammation. By improving glucose uptake in skeletal muscle and minimizing catabolic stressors, tirzepatide supports muscle integrity and function during periods of caloric deficit. This makes it a potentially valuable adjunct for athletes aiming to achieve fat loss without compromising strength or recovery [14,18,19].

Impact on Muscle Quality

Emerging evidence suggests that tirzepatide may directly enhance muscle quality by promoting anabolic pathways and inhibiting catabolic processes. GLP-1 receptor activation has been shown to augment muscle protein synthesis by improving insulin signaling and nutrient delivery to muscle tissues. Additionally, tirzepatide's anti- inflammatory properties play a crucial role in maintaining muscle health. Chronic inflammation, often exacerbated by intense training regimens, impairs muscle recovery and increases the risk of overtraining syndromes. By reducing pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), tirzepatide supports faster recovery and improves muscle resilience [11,14,17].

Further, preclinical and emerging clinical data suggest that tirzepatide may improve muscle contractile function and power metrics. This is potentially mediated by enhanced mitochondrial efficiency and reduced intramuscular fat infiltration, both of which contribute to superior muscle performance. For athletes in strength- and power- based disciplines, these effects may translate to improved metrics such as sprint times, lifting capacity, and explosive force generation [13,20].

Potential Implications for Athletic Performance

Enhanced Endurance

Tirzepatide holds significant promise for endurance athletes due to its ability to optimize fat metabolism, a critical determinant of prolonged aerobic performance. By promoting fat oxidation, tirzepatide delays the depletion of glycogen stores, a limiting factor in sustained exercise. This glycogen-sparing effect allows athletes to maintain higher intensities over longer durations. Mechanistically, tirzepatide enhances mitochondrial function and stimulates mitochondrial biogenesis—key processes in efficient energy production. Improved

mitochondrial density and activity increase the capacity for oxidative phosphorylation, the primary energy system utilized during endurance events such as long-distance running, cycling, and swimming [22,26].

Studies further suggest that GIP receptor activation contributes to increased thermogenesis and lipid utilization, effectively shifting the body's energy preference toward fat substrates during prolonged activity. This adaptation improves not only the athlete's capacity to perform but also overall metabolic efficiency, which is essential in sports requiring consistent output over extended periods [23].

Improved Recovery

Recovery is a cornerstone of athletic performance, particularly for athletes engaged in high-intensity or repeated competition. Tirzepatide's dual anti-inflammatory and metabolic effects position it as a valuable adjunct for optimizing recovery. By reducing systemic inflammation, including markers such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), tirzepatide mitigates muscle damage and oxidative stress caused by intense physical exertion [24,25].

In addition, improved glucose uptake and glycogen replenishment are critical for rapid recovery. GLP-1 receptor activation facilitates insulin-mediated glucose transport into muscle cells, accelerating the restoration of energy reserves post-exercise. This is particularly relevant for athletes who undergo multiple training sessions per day or compete in tournaments requiring short recovery windows. Enhanced recovery not only reduces fatigue but also minimizes the risk of overtraining syndrome, a condition detrimental to performance and long-term athletic health [25].

Metabolic Flexibility

Metabolic flexibility, or the ability to efficiently transition between energy substrates such as fats and carbohydrates, is a critical determinant of athletic success. Tirzepatide's ability to improve insulin sensitivity directly enhances this metabolic adaptability. For athletes, this translates into seamless shifts between aerobic and anaerobic energy systems during varying intensities of exercise, such as interval training or sports requiring frequent bursts of power [27].

By enhancing substrate utilization, tirzepatide allows for more efficient ATP production under both oxidative and glycolytic conditions. This is particularly advantageous in mixed sports, such as soccer, basketball, and CrossFit, where athletes must sustain prolonged aerobic effort while executing short bursts of anaerobic activity. Additionally, the reduction in visceral adiposity observed with tirzepatide therapy reduces the metabolic burden on insulin signaling pathways, further improving the athlete's capacity to utilize energy efficiently under competitive conditions [23,27,28].

Ethical Considerations and Use in Sports

Potential for Misuse

Athletes without medical justification might use tirzepatide to gain a competitive edge, exploiting its benefits in
weight loss, fat oxidation, and endurance enhancement. However, such off-label use raises considerable risks, including gastrointestinal side effects, metabolic dysregulation, and potential interference with the body’s natural hormonal balance. Long-term misuse could also predispose individuals to health complications, such as hypoglycemia or impaired gut motility, especially in the absence of clinical oversight [30,31].

Beyond physiological risks, widespread misuse of tirzepatide in sports could create systemic problems, such as normalization of pharmacological performance enhancement. This could lead to pressures on athletes to adopt similar measures to remain competitive, fostering a cycle of dependence on unregulated use of metabolic drugs [31].

Regulatory Status

Tirzepatide is not currently classified as a prohibited substance by the World Anti-Doping Agency (WADA). However, its profound metabolic benefits and potential to influence performance metrics could prompt future regulatory scrutiny. WADA's consideration of tirzepatide for inclusion on the prohibited list would depend on its classification as a performance-enhancing agent, specifically whether its effects significantly alter competitive fairness.

The dual agonism of GLP-1 and GIP receptors is not inherently associated with performance enhancement but could be viewed as providing an "unfair advantage" in disciplines where body composition and recovery play pivotal roles. Should clinical evidence confirm performance-enhancing effects in healthy athletes, regulatory bodies may respond by introducing restrictions, requiring clear demarcation of therapeutic versus non-therapeutic use. This situation would parallel earlier discussions surrounding other metabolic enhancers like erythropoietin (EPO) or beta-2 agonists [30,32].

Equity and Fairness

The availability of tirzepatide introduces profound ethical questions about equity in sports. Access to such pharmacological aids could disproportionately benefit athletes with greater financial or institutional support, particularly in weight-class disciplines like boxing, wrestling, and mixed martial arts. By enabling significant fat loss and improved recovery, tirzepatide could amplify disparities between those with access to advanced medical treatments and those without.

Moreover, reliance on pharmacological interventions for performance enhancement undermines the fundamental principles of sport, including natural ability, discipline, and effort. The normalization of tirzepatide use among healthy athletes risks eroding the integrity of competition, creating a landscape where success is increasingly dependent on biomedical interventions rather than training or talent. This challenges not only fairness but also the spirit of sport as defined by international regulatory frameworks [31,32].

Conclusion

Tirzepatide represents a groundbreaking advancement in the treatment of type 2 diabetes, obesity, and metabolic health, with potential applications in athletic performance. Its dual action on the GLP-1 and GIP receptors allows it to target multiple metabolic pathways simultaneously, offering significant benefits in body composition, weight loss, and insulin sensitivity. While tirzepatide's effects on athletic performance are promising, ethical concerns regarding its use in competitive sports must be addressed, particularly with regard to anti-doping regulations. Further research is needed to fully understand the drug's long-term impact on athletic performance, muscle mass, and overall metabolic health in healthy individuals.

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