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An Integrated Approach to Obesity Management: Clinical Synergy Between GLP-1 Receptor Agonists and Sports Medicine. A Narrative Review

Julia Kociuba

LUX MED Sp. z o.o.

Szturmowa 2, 02-678 Warszawa

ORCID: 0009-0001-9030-0108

julia.kociuba@wp.pl

Zuzanna Kruczek

SP ZOZ MSWiA in Rzeszów
Krakowska 16, 35-111 Rzeszów
ORCID: 0009-0008-6153-1995
zuzanna.kruczek@op.pl

Martyna Kudła

University Clinical Hospital No. 4 in Lublin
Doktora Kazimierza Jaczewskiego 8, 20-954 Lublin
ORCID: 0009-0007-7465-5199
mkudla20@gmail.com

Agata Krawczyk

University Clinical Hospital No. 4 in Lublin
Doktora Kazimierza Jaczewskiego 8, 20-954 Lublin
ORCID: 0009-0004-8883-3572
agata.krawczyk0137@gmail.com

Natalia Pawelczak

Health Care Facility of the Ministry of Interior and Administration in Lublin
Granadierów 3, 20-331 Lublin
ORCID: 0000-0001-9933-258X
n.pawelczak@student.uw.edu.pl

Dorota Kolkowicz

Provincial Specialist Hospital in Wrocław
Henryka Michała Kamińskiego 73A, 51-124 Wrocław
ORCID: 0009-0001-3410-4401
dorotakolkowicz@gmail.com

Paweł Czechowicz

University Hospital in Krakow
Marii Orwid 11; 30-688 Kraków
ORCID: 0009-0008-0143-0404
pawel.czechowicz2000@gmail.com

Justyna Czechowicz

Stefan Żeromski Specialist Hospital in Krakow
Osiedle na Skarpie 66; 31-913 Kraków
ORCID: 0009-0003-1035-1648
justyna.barycz12@gmail.com

Mikołaj Antkiewicz

Ludwik Rydygier Specialist Hospital in Krakow sp. z o.o.
Osiedle Złotej Jesieni 1, 31-820 Kraków
ORCID: 0009-0000-8735-9339
miki.antek2000@gmail.com

Aleksandra Arczyńska-Antkiewicz

Jagiellonian University Collegium Medicum
Świętej Anny 12, 31-008 Kraków
ORCID: 0009-0008-0410-4751
aaarczynska@gmail.com

Maria Drozd

Ludwik Rydygier Specialist Hospital in Krakow sp. z o.o.
Osiedle Złotej Jesieni 1, 31-820 Kraków
ORCID: 0009-0001-4246-4095
mariadrozd22@gmail.com

Paulina Łobaza

Medical Center in Łańcut Sp z o.o.
Ignacego Paderewskiego 5, 37-100 Łańcut
ORCID: 0009-0003-3566-005X
paulina.lobaza@gmail.com

Szymon Kurciński

1st Military Clinical Hospital with Outpatient Clinic in Lublin
al. Raławickie 23, 20-049 Lublin
ORCID: 0009-0001-9157-854X
szymonkurcinski.med@gmail.com

Julia Kurcińska

University Clinical Hospital No. 4 in Lublin
Doktora Kazimierza Jaczewskiego 8, 20-954 Lublin
ORCID: 0009-0003-4008-4245
j.14@wp.pl

Gabriela Zając

Szpital Uniwersytecki w Krakowie
Marii Orwid 11; 30-688 Kraków
ORCID: 0009-0009-9222-2711
gabrielazajac.zajac@student.uj.edu.pl

Corresponding author: Julia Kociuba, julia.kociuba@wp.pl

ABSTRACT

Background. Obesity is a complex neuroendocrine disease requiring long-term management. The emergence of GLP-1 receptor agonists has revolutionized weight loss outcomes; however, pharmacological monotherapy often leads to significant lean body mass (LBM) loss and metabolic adaptation.

Aim. To analyze the clinical synergy between incretin-based pharmacotherapy and sports medicine protocols, focusing on functional tissue preservation and long-term metabolic health.

Material and methods. A comprehensive review of scientific literature (2021–2026) was conducted, incorporating data from phase III clinical trials (STEP, SURMOUNT, SELECT) and exercise physiology research during pharmacological weight loss.

Results. GLP-1 RA monotherapy results in LBM loss comprising 20–40% of total weight reduction. Structured resistance and aerobic training mitigates this loss, enhances muscle quality, and preserves bone mineral density. Combined therapy achieves superior visceral fat reduction and attenuates systemic inflammation while maintaining a higher basal metabolic rate compared to pharmacotherapy alone.

Conclusions. Integrating sports medicine with modern pharmacotherapy represents a new standard in obesity treatment. Physical activity serves as a "metabolic anchor," preventing weight regain and improving patients' health-related quality of life (HRQoL).

Keywords: obesity, GLP-1 receptor agonists, sports medicine, lean body mass, metabolic synergy

1. Introduction: The Evolution of Obesity Management and GLP-1 RAs

Obesity has emerged as one of the most significant global public health challenges of the 21st century, characterized by a chronic, relapsing disease state that predisposes individuals to a multitude of metabolic and cardiovascular complications. For decades, the cornerstone of obesity treatment was restricted to lifestyle interventions - primarily caloric restriction and increased physical activity. However, the long-term success of these interventions alone remained limited due to powerful biological counter-regulatory mechanisms, such as increased hunger hormones and a slowing metabolic rate, which consistently drive weight regain.

1.1. The Shift in Pharmacological Paradigms: STEP and SURMOUNT

The landscape of obesity management underwent a radical shift with the clinical validation of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs). Originally designed for the treatment of Type 2 Diabetes Mellitus, these incretin mimetics demonstrated profound weight-loss efficacy by targeting central appetite regulation.

The landmark STEP 1 trial was a pivotal moment in this evolution [1]. In this double-blind, randomized controlled trial involving 1,961 adults, participants receiving a weekly 2.4 mg dose

of subcutaneous semaglutide achieved an average body weight reduction of 14.9% over 68 weeks, compared to just 2.4% in the placebo group. This study proved that pharmacological intervention could achieve weight loss results previously only seen with surgical procedures. Following the success of semaglutide, the introduction of dual-agonist therapies further pushed the boundaries of medical weight loss. The SURMOUNT-1 trial evaluated tirzepatide, a novel molecule targeting both GLP-1 and Glucose-dependent Insulinotropic Polypeptide (GIP) receptors [2]. The results were unprecedented, with the highest dose yielding an average weight reduction of 20.9% over 72 weeks. These findings confirmed that incretin-based drugs effectively bridge the gap between conventional lifestyle changes and bariatric surgery [3].

1.2. Mechanism of Action: The Incretin Effect and Beyond

The physiological basis of GLP-1 RAs lies in their ability to mimic endogenous GLP-1, a peptide hormone secreted by the L-cells of the distal ileum in response to nutrient ingestion. GLP-1 physiology is complex; it functions by potentiating glucose-dependent insulin secretion (the incretin effect), suppressing glucagon release, and significantly slowing gastric emptying, which prolongs the sensation of postprandial fullness [4].

Crucially, GLP-1 receptors are widely distributed in the central nervous system, particularly in the hypothalamus and the hindbrain, where they directly modulate satiety and reduce "food noise"—the intrusive, constant thoughts about eating that plague many individuals with obesity [3, 4]. Furthermore, the therapeutic scope of these agents extends to cardiovascular health. By reducing systemic inflammation, improving endothelial function, and modulating the autonomic nervous system, GLP-1 RAs provide significant cardiovascular benefits that occur both as a result of and independently of weight loss [5].

1.3. The Scientific Problem: Quantity vs. Quality of Weight Loss

Despite the clinical triumphs of semaglutide and tirzepatide, a critical concern has emerged regarding the "composition" of weight loss. Rapid reduction in body mass is frequently associated with a significant loss of lean body mass (LBM), which includes skeletal muscle and bone mineral density.

This creates a vital intersection for the field of Sports Medicine. While GLP-1 RAs effectively manage the hormonal and neurological drivers of obesity, they do not inherently provide the mechanical stimuli necessary to maintain musculoskeletal integrity. This review aims to explore how structured physical activity—specifically resistance and aerobic training—can act

as a synergistic partner to pharmacology, ensuring that weight loss is "healthy," sustainable, and functionally beneficial for the patient.

2. Pathophysiological Synergy: Metabolism, Cardiovascular System, and Mitochondria

The clinical landscape of obesity treatment has been redefined by GLP-1 RAs, yet the physiological maximum of these drugs is only reached when they operate in tandem with physical exercise. This synergy is not merely a combination of two independent weight-loss methods; it is a complex pathophysiological "cross-talk" where exercise provides the mechanical and metabolic signals that stabilize and enhance the pharmacological effects of incretin mimetics [6].

2.1. Convergent Pathways in Glucose Metabolism and Insulin Sensitivity

The primary metabolic synergy lies in the potentiation of glucose disposal through two distinct but converging pathways. GLP-1 RAs improve glycemic control through the hormonal axis—enhancing glucose-dependent insulin secretion from pancreatic beta cells and suppressing inappropriate glucagon release from alpha cells. However, in patients with chronic obesity, hormonal signaling alone often faces the hurdle of systemic insulin resistance.

This is where physical activity becomes a mandatory partner. Exercise serves as the most potent non-pharmacological stimulus for GLUT4 translocation via the AMPK pathway, which remains functional even when the insulin-signaling pathway is impaired. Research utilizing a randomized controlled trial design demonstrated that this "double-hit" effect leads to a reduction in the severity of metabolic syndrome that is significantly more robust than with monotherapy [7]. The study specifically noted that the combination of exercise and GLP-1 RAs led to a twice as large reduction in body fat mass compared to the drug-only group, primarily by targeting visceral adiposity and reducing systemic low-grade inflammation.

2.2. Cardiovascular Resilience and the "Functional Gap"

The cardiovascular benefits of GLP-1 RAs represent one of the most significant breakthroughs in modern metabolic medicine. These agents function as far more than "weight loss drugs"; they exert direct cardioprotective effects by improving endothelial function, reducing myocardial oxidative stress, and modulating the autonomic nervous system [8]. The landmark SELECT trial solidified this position, proving a 20% reduction in major adverse cardiovascular events (MACE) in a broad population of patients with obesity [9].

However, a "functional gap" remains: pharmacological weight loss can lead to a reduction in absolute VO₂ max and stroke volume due to the rapid decrease in total body mass and blood volume. Evidence emphasizes that while the drug protects the heart chemically, only physical activity can close this gap by improving myocardial contractility and peripheral oxygen extraction [10]. Without exercise, the patient may become "lighter" but not necessarily "fitter" or more resilient to hemodynamic stress.

Table 1: Pathophysiological Interaction between GLP-1 RAs and Physical Exercise.

Physiological System	GLP-1 RA Mechanism	Exercise-Induced Mechanism	Synergistic Clinical Outcome
Glucose Metabolism	↑Glucose-dependent insulin secretion; ↓Glucagon release [7]	↑ GLUT4 translocation via AMPK-mediated pathway [10]	Restoration of metabolic flexibility and glycemic stability.
Cardiovascular	↓Endothelial protection; ↓Myocardial oxidative stress [8, 9]	↑ Stroke volume; ↑ Capillary density in skeletal muscle [6, 10]	Optimized cardiorespiratory fitness (VO ₂ max) and hemodynamic resilience.
Inflammation	↓ Systemic pro-inflammatory cytokines [7, 12]	Modulation of myokines and immune function [11]	Potent anti-inflammatory environment; reversal of metabolic syndrome.
Adipose Tissue	Central suppression of appetite; ↓ Visceral fat mass [6, 9]	↑ Lipolysis and fat oxidation; Potential WAT "browning" [7, 11]	Targeted reduction of ectopic fat and visceral adiposity.

Metabolic Rate	Risk of BMR decline due to rapid mass loss [11]	Maintenance of BMR through mechanical loading and muscle sparing [11, 12]	Prevention of metabolic adaptation; long-term weight maintenance.
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Abbreviations: AMPK – Adenosine monophosphate-activated protein kinase; BMR – Basal Metabolic Rate; GLP-1 RA – Glucagon-Like Peptide-1 Receptor Agonist; GLUT4 – Glucose transporter type 4; VO2 max – Maximal oxygen consumption; WAT – White Adipose Tissue.

2.3. Resistance Training as a Metabolic Stabilizer

A major pathophysiological risk of potent GLP-1 RA therapy is the potential for a "metabolic crash" caused by the loss of active metabolic tissue. Evidence suggests that resistance exercise provides the critical "anabolic counter-signal" necessary to navigate this risk. By creating mechanical tension and activating the mTOR pathway, resistance training ensures that the body prioritizes the preservation of skeletal muscle during the hypocaloric state induced by the drug [11]. This preservation of muscle mass is the primary determinant of the Basal Metabolic Rate (BMR), ensuring that the patient does not experience the severe metabolic adaptation that often leads to weight loss plateaus.

2.4. Post-Treatment Resilience and the "Metabolic Anchor"

The most daunting challenge in obesity management is the "rebound effect" following pharmacological cessation. The pathophysiological synergy of exercise provides a unique solution to this problem. A detailed post-treatment analysis conducted one year after stopping GLP-1 RA therapy yielded definitive findings: participants who had integrated a structured exercise routine during the active treatment phase were significantly more successful at maintaining their lower weight and metabolic health one year later [12]. Exercise appears to act as a "metabolic anchor," resetting the body's physiological set-point and providing the neurobiological and metabolic resilience required to resist weight regain once the pharmacological "crutch" is removed.

3. The "Quality of Weight Loss": Body Composition, Muscle Integrity, and Sarcopenia

In the clinical management of obesity, the magnitude of weight loss often overshadows the more critical parameter of body composition. From a sports medicine perspective, the success of GLP-1 RA therapy is defined not by the total kilograms lost, but by the ratio of adipose tissue reduction to the preservation of lean body mass (LBM). Rapid weight reduction without physiological counter-signals poses a significant risk to musculoskeletal health, basal metabolic rate (BMR), and long-term metabolic stability.

3.1. The Lean Body Mass (LBM) Paradox and Sarcopenic Risk

Clinical evidence from high-potency incretin trials suggests a concerning trend regarding the "quality" of mass reduction. Weight loss induced by semaglutide and tirzepatide is never adipose-exclusive; LBM loss can account for a substantial portion—often estimated between 20% and 40%—of the total weight reduction [13]. This loss includes not only skeletal muscle but also extracellular water and connective tissues.

This phenomenon, often termed the "LBM paradox," is primarily driven by the profound caloric deficit. GLP-1 RAs suppress appetite so effectively that patients often fall below the protein threshold required to maintain a positive nitrogen balance. Evidence suggests that while some loss of non-fat mass is a normal physiological response to a lower body weight, an excessive loss of contractile skeletal muscle is maladaptive. This can lead to "sarcopenic obesity," a condition where the individual has a lower body weight but a diminished metabolic rate and impaired functional strength. This state significantly increases the risk of the "yo-yo effect" once the pharmacological treatment is discontinued, as the body's primary engine for energy expenditure has been compromised [14].

3.2. Functional Muscle Integrity and the SEMALEAN Insights

It is essential to distinguish between muscle quantity and muscle quality. Obesity is frequently characterized by myosteatosis—the infiltration of lipids into muscle fibers—which impairs force production, mitochondrial efficiency, and insulin signaling.

Critical insights into this distinction were provided by the SEMALEAN study. By utilizing advanced imaging and functional testing, researchers demonstrated that although total muscle volume might decrease during semaglutide therapy, the muscle quality (defined as strength per unit of cross-sectional area) can be preserved or even improved, provided the patient avoids complete physical inactivity [15]. This suggests that GLP-1 RAs might actually help "cleanse"

the muscle of ectopic fat, but the maintenance of the muscle fibers themselves requires the mechanical stimulus of exercise.

However, clinical observations issue a cautionary note, emphasizing that fundamental body composition principles must remain at the forefront of monitoring. For older adults or individuals with baseline low muscle mass, the loss of LBM can cross a critical threshold, leading to physical frailty and a reduced capacity for glucose disposal, as skeletal muscle remains the body's primary site for postprandial glucose uptake and insulin-mediated action [16].

3.3. Resistance Training: The Anabolic Counter-Signal to mTOR Suppression

The only effective physiological strategy to mitigate LBM loss during medical weight loss is the implementation of structured resistance training (RT). On a molecular level, the caloric restriction induced by GLP-1 RAs can suppress the mTOR (mammalian target of rapamycin) pathway, the primary driver of muscle protein synthesis. RT acts as a mandatory "anabolic counter-signal," utilizing mechanical tension to re-activate mTOR and protein translation even in a hypocaloric state.

Comprehensive systematic reviews and meta-analyses covering the lifespan of individuals with obesity have established that resistance training is the most effective intervention for optimizing body composition [17]. Findings indicate that RT not only spares lean mass but also enhances the reduction of body fat percentage more effectively than aerobic exercise alone. By maintaining LBM, RT serves as a "metabolic insurance policy," keeping the BMR elevated and preventing the severe metabolic adaptation that typically follows rapid weight loss.

3.4. Skeletal Health and Bone Mineral Density (BMD) Protection

An often-overlooked consequence of rapid weight reduction is the impact on bone turnover and skeletal integrity. The skeleton is a highly mechanosensitive organ; losing 15% to 20% of body weight significantly reduces the gravitational load on the femur and lumbar spine, which can lead to increased osteoclast activity.

A secondary analysis of a randomized clinical trial specifically focusing on bone health during weight loss maintenance revealed that while GLP-1 RA therapy alone might lead to a measurable decrease in bone mineral density at the hip and spine, the combination with exercise—specifically weight-bearing and resistance activities—completely mitigated this effect [18]. This ensures that the patient's "scaffolding" remains intact, reducing the long-term risk of osteoporotic fractures.

Table 2: Impact of Intervention Type on Body Composition and Tissue Health

Outcome Metric	GLP-1 RA Monotherapy	GLP-1 RA + Resistance Training
Fat Mass Loss [13, 17]	High (Systemic)	Very High (Synergistic)
LBM Preservation [13, 14, 15]	Low (20–40% loss)	High (Sparing effect)
Muscle Quality [15]	Variable	Improved (↓ Myosteatosis)
Metabolic Rate [14, 17]	Significant Decline	Optimized/Maintained
Bone Density [18]	Potential Decrease	Protected (Mechanical Load)
Functional Strength [15, 17]	Potential Decrease	Significant Increase
Fat Mass Loss [13, 17]	High (Systemic)	Very High (Synergistic)

Abbreviations: LBM – Lean Body Mass; GLP-1 RA – Glucagon-Like Peptide-1 Receptor Agonist.

Critical Synthesis of Table 2: The Musculoskeletal-Metabolic Interdependency

The comparative data summarized in Table 2 highlights a critical physiological divergence between pharmacological monotherapy and the integrated sports medicine model. While GLP-1 RA therapy demonstrates high efficacy in reducing total systemic fat mass, the "pharmacology-only" approach introduces a state of musculoskeletal vulnerability.

A primary concern reflected in the evidence is the disproportionate loss of lean body mass (LBM). Findings indicate that the rapid weight reduction achieved through incretin signaling alone often bypasses the body's natural protein-sparing mechanisms, leading to a significant reduction in contractile tissue [13, 14]. This loss is not merely a change in aesthetics; it represents a decline in the body's primary site for glucose disposal and a potential collapse of the basal metabolic rate.

Conversely, the integration of resistance training (RT) acts as a mandatory metabolic buffer. By providing the mechanical stimulus necessary to counteract the catabolic effects of a

profound caloric deficit, RT shifts the composition of weight loss toward a near-exclusive reduction of adipose tissue [17]. This synergy is further exemplified by the results of the SEMALEAN study, which suggests that the "active" patient experiences a qualitative improvement in muscle function (reduced myosteatosis and increased strength-to-mass ratio), even when absolute muscle volume is slightly reduced [15].

Furthermore, the protection of bone mineral density (BMD) serves as a vital clinical endpoint. Analyses underscore that the mechanical unloading of the skeleton during rapid weight loss is a significant risk factor for bone resorption. The data suggests that exercise-induced osteogenic loading is the only intervention capable of maintaining skeletal integrity during high-magnitude weight loss [18]. In summary, the transition from GLP-1 RA monotherapy to a combined intervention represents a shift from "mass reduction" to "functional metabolic restoration."

4. Health-Related Quality of Life (HRQoL): Psychological and Functional Outcomes

The success of obesity management has traditionally been measured by objective markers such as kilograms lost or reduction in waist circumference. However, from a patient-centered perspective, the most meaningful outcomes are often related to Health-Related Quality of Life (HRQoL). For individuals undergoing treatment with GLP-1 RAs, the pharmacological intervention does not only enhance physiological parameters but also profoundly impacts psychological resilience, social functioning, and perceived physical capability.

4.1. Functional Gains and the SF-36 Framework

One of the most comprehensive evaluations of patient-reported outcomes comes from the STEP clinical program. Analysis of these results indicates that semaglutide treatment leads to "wider benefits" that extend far beyond simple weight loss. Utilizing the SF-36 (Short Form-36) Health Survey, researchers identified significant improvements across multiple domains, particularly in physical functioning and vitality [19]. Patients reported a marked reduction in bodily pain and a significant increase in energy levels, which directly impacts their willingness to engage in physical activity. From a sports medicine perspective, these gains are critical, as they lower the "barrier to entry" for structured exercise programs by reducing the perceived effort of movement.

4.2. Dose-Response Relationship in Quality of Life: SURMOUNT Insights

The magnitude of weight loss achieved with dual agonists like tirzepatide has shown a direct correlation with the degree of improvement in quality of life. Results from the SURMOUNT-1

study demonstrate that improvements in the IWQOL-Lite-CT (Impact of Weight on Quality of Life-Lite Clinical Trials) scores are dose-dependent [20]. Participants achieving higher weight loss thresholds experienced disproportionately greater gains in self-esteem and work-related productivity. This suggests that the pharmacological potency of the drug provides a "psychological re-entry" into social life, mitigating the weight-related stigma that often prevents individuals with obesity from participating in community-based physical activities.

4.3. The Psychological Impact of Treatment Withdrawal

A critical challenge in long-term obesity management is the maintenance of psychological well-being after the acute weight-loss phase. The STEP 4 trial provided pivotal data on the effects of treatment interruption: patients who switched from semaglutide to placebo experienced not only a rapid regain of weight but also a statistically significant decline in their HRQoL scores [21]. This highlights that the psychological benefits of therapy are closely tied to the metabolic and neurobiological stability provided by continuous GLP-1 receptor activation.

Furthermore, analysis of the SURMOUNT-3 results emphasizes that while intensive lifestyle interventions are foundational, the added pharmacological support allows patients to achieve a "functional threshold" where daily activities no longer feel burdensome [22]. This state of "effortless movement" is essential for maintaining high mental health subscores and preventing the burnout often associated with long-term weight management.

4.4. Cognitive Unloading and the "Food Noise" Phenomenon

A unique neuropsychological aspect of GLP-1 RA therapy is its impact on the brain's reward centers. Exploration of the psychological dimension of these drugs noted a dramatic reduction in "food noise"—the obsessive, intrusive thoughts about eating and constant cravings [23]. For many patients, this represents a "cognitive unloading" that is just as important as the physical weight loss. By silencing the central nervous system's preoccupation with caloric intake, GLP-1 RAs allow for a behavioral reset, enabling patients to focus their mental energy on performance-based goals and skill acquisition in their exercise routines.

4.5. Symptomatic Relief in Complex Clinical Cases

The intersection of cardiovascular health and subjective well-being was clearly demonstrated in the STEP-HFpEF trial. In patients suffering from heart failure with preserved ejection fraction and obesity, semaglutide significantly improved scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ-CSS) [24]. This finding proves that the drug's effects

translate directly into symptomatic relief; participants reported fewer physical limitations and a reduction in fatigue and shortness of breath during daily life. This symptomatic improvement is the primary driver of increased physical activity in complex patient populations, creating a bridge between medical stabilization and functional restoration.

5. Practical Applications in Sports Medicine: Integrated Protocols

The integration of GLP-1 RAs into clinical practice requires a fundamental paradigm shift in sports medicine. Rather than viewing exercise as a secondary "weight loss tool," it must be repositioned as a primary "metabolic stabilizer" and "tissue protector." This chapter outlines the practical frameworks for combining pharmacological therapy with structured physical activity to maximize long-term health outcomes and ensure functional longevity.

5.1. Lifestyle Prioritization and the "Window of Opportunity"

The rapid suppression of appetite and initial weight loss provided by GLP-1 RAs create a unique "window of opportunity." Evidence suggests that the reduction in weight-related joint pain and the psychological boost from early success significantly increase a patient's readiness for physical activity [25]. The core of this approach is "lifestyle prioritization"—using the drug as a facilitator to build the physical capacity and behavioral habits necessary for a life without constant pharmacological dependency.

In this model, the medication serves as the scaffold, while exercise serves as the structural foundation of the patient's new metabolic set-point. Clinicians should capitalize on the early "energy surge" often reported by patients after the initial weight-loss phase to introduce more complex movement patterns and habit-forming routines.

5.2. Nutritional Synergy and Protein-Sparing Exercise Protocols

A significant risk identified in previous chapters is the loss of lean body mass (LBM). To mitigate this, sports medicine practitioners must implement "protein-sparing" strategies that synchronize nutrition with mechanical loading. Research demonstrates that the combination of exercise and GLP-1 RA treatment leads to superior weight loss maintenance compared to either intervention alone, provided that the physical activity is sufficient to maintain a high metabolic rate [26].

Practical protocols should prioritize:

- Resistance Training (RT): Minimum of 2–3 sessions per week targeting major muscle groups to counteract the catabolic effects of caloric restriction.
- Protein Timing: Ensuring adequate protein intake (1.6–2.2g/kg of LBM) in the peri-workout window to stimulate muscle protein synthesis despite suppressed general appetite.
- Monitoring: Using functional strength tests (e.g., grip strength or 1RM estimations) to ensure that the patient is losing fat, not functional capacity.

5.3. Reversing Metabolic Syndrome and Managing Inflammation

The clinical application of GLP-1 RAs extends to the deep reversal of the inflammatory state associated with obesity. Evidence highlights that combination therapy is more effective at reducing abdominal obesity and systemic inflammatory markers (such as CRP) than monotherapy [27].

For the sports medicine clinician, this reduction in systemic inflammation has profound implications for recovery. Patients on GLP-1 RAs may experience improved recovery times between sessions, allowing for a gradual increase in training volume. However, clinicians must also be mindful of the drug's impact on heart rate; these agents are known to slightly increase resting heart rate, necessitating careful monitoring of heart rate variability (HRV) and perceived exertion (RPE) during high-intensity sessions to prevent overtraining.

5.4. Immunological Protection and Mitochondrial Quality Control

The pharmacological profile of GLP-1 RAs provides a protective effect that complements the benefits of aerobic exercise. These agents possess potent anti-inflammatory and immunological properties that may enhance the body's response to physical stress and reduce the risk of obesity-related chronic inflammation [28].

This synergy is particularly relevant for mitochondrial health. While GLP-1 RAs reduce oxidative stress and improve the "internal environment" of the cell, exercise remains the primary stimulus for mitochondrial biogenesis. A mixed-modality program—incorporating "Zone 2" aerobic training to improve mitochondrial efficiency and fat oxidation—is essential. This ensures that the patient's metabolic flexibility is restored, making them more resilient to future caloric fluctuations.

5.5. The "Metabolic Anchor" and Long-term Maintenance

The ultimate goal of sports medicine intervention in this context is to prepare the patient for potential pharmacological cessation. The combination of exercise and GLP-1 RAs has been shown to be the most effective strategy for preventing the "rebound effect" [26, 27]. By building a substantial foundation of muscle mass and improving cardiorespiratory fitness, the patient creates a "metabolic anchor." This anchor stabilizes the body at a lower weight set-point, providing the physiological and psychological resilience required to maintain health long after the active pharmacological phase has concluded.

6. Discussion: Sustaining Weight Loss Post-Cessation

6.1. The "Pharmacology Only" Trap and Global Guidelines

The comparison between "Pharmacology only" and "Pharmacology + Lifestyle" groups reveals a critical divergence in clinical success. Patients in pharmacology-only groups typically experience rapid weight reduction; however, as reinforced by comprehensive clinical guidelines, this cohort remains highly susceptible to the "rebound effect" upon drug cessation [29]. Without the behavioral and physiological scaffolding provided by sports medicine, the weight loss achieved is often "metabolically fragile," as the reduction in basal metabolic rate creates a physiological environment prone to weight regain.

6.2. Comparative Analysis of Withdrawal Outcomes

Recent evidence suggests that the rate of weight regain is significantly accelerated in patients who did not meet a minimum threshold of resistance training during the active pharmacological phase. Narrative reviews of randomized studies indicate that interrupting treatment with liraglutide, semaglutide, or tirzepatide without a structured maintenance protocol often leads to a rapid reversal of metabolic benefits [30]. Long-term weight maintenance is fundamentally dependent on sustained lifestyle and habit changes rather than pharmacological intervention alone, underscoring that structured physical activity must be considered a non-negotiable pillar of post-cessation obesity management [31]. This reinforces the necessity of the "active weight loss" model as an essential exit strategy from chronic pharmacotherapy.

i. 6.3. Physical Performance as a Clinical Biomarker

Expanding on the necessity of integrated protocols, recent research highlights that the preservation of muscle quality and functional strength is the primary predictor of long-term success. Comprehensive reviews demonstrate that patients who engage in structured resistance

training while on GLP-1 RAs show significantly higher VO2 max and power-to-weight ratios compared to those on medication alone [32]. Therefore, "physical performance" should be treated as a clinical biomarker of successful, long-term obesity remission rather than just a secondary benefit of treatment.

7. Conclusions

The paradigm shift in obesity management, catalyzed by the advent of GLP-1 and dual GLP-1/GIP receptor agonists, represents one of the most significant advancements in metabolic medicine. However, the evidence synthesized in this review underscores that pharmacological potency alone is insufficient for the comprehensive restoration of health. The transition from "passive weight loss" to a multi-disciplinary "active weight loss" protocol is essential for long-term clinical success.

Based on the analysis of current clinical trials and physiological data, the following conclusions can be drawn:

7.1. The Necessity of the Integrated Synergy

While agents such as semaglutide and tirzepatide demonstrate unprecedented efficacy in reducing total body mass, they lack the intrinsic ability to modulate musculoskeletal quality. The synergy between pharmacology and sports medicine is not merely additive; it is a clinical requirement. Pharmacotherapy effectively bypasses the neurobiological barriers to weight loss (e.g., "food noise" and hormonal resistance), while structured physical activity provides the mechanical stimuli necessary to protect the metabolic engine of the body—the skeletal muscle.

7.2. Preservation of Lean Body Mass as a Clinical Priority

The loss of lean body mass (LBM), which can reach up to 40% of total weight loss in pharmacological monotherapy, represents a significant risk to the patient's metabolic future. Resistance training stands as the gold-standard intervention to counteract this effect. By maintaining the basal metabolic rate and preserving bone mineral density, sports medicine interventions ensure that the "quality" of weight loss is optimized, thereby reducing the risk of sarcopenic obesity and functional frailty, particularly in aging populations.

7.3. Psychological Resilience and Cognitive Unloading

The reduction of "food noise" provided by GLP-1 RAs creates a unique psychological "clarity" that facilitates long-term behavioral change. This cognitive unloading allows patients to shift their focus from the struggle against cravings to the mastery of physical performance. The resulting improvements in Health-Related Quality of Life (HRQoL) are more sustainable when patients experience the tangible, functional gains associated with improved cardiorespiratory fitness and strength.

7.4. Long-term Stability and the "Metabolic Anchor"

The most daunting challenge in obesity treatment remains the high rate of weight regain after pharmacological cessation. The integration of exercise during the active treatment phase serves as a "metabolic anchor," resetting the body's physiological set-point and building the structural resilience required to maintain weight loss. Habit formation and physiological adaptations (such as increased mitochondrial density and improved insulin sensitivity) are the primary determinants of post-treatment success.

7.5. Future Directions in Clinical Practice

The future of obesity care must prioritize "Lifestyle Prioritization" protocols. Clinicians should view GLP-1 RAs as a powerful tool to initiate metabolic change, but exercise remains the primary modality for maintaining it. Moving forward, the development of precision exercise prescriptions, tailored to the specific pharmacological profile of the patient, will be essential to maximize the benefits of these life-changing therapies while minimizing their risks.

Final Synthesis Statement

In summary, the era of treating obesity as a simple caloric imbalance is over. We have entered the era of precision metabolic medicine, where the synergy between advanced pharmacology and evidence-based sports science offers the first real possibility of sustained, health-focused weight management. For the patient, this means not just a lower weight on the scale, but a fundamental restoration of functional capacity, metabolic flexibility, and quality of life.

Disclosure

Author Contributions:

Conceptualization: Julia Kociuba, Zuzanna Kruczek, Martyna Kudła, Szymon Kurciński

Methodology: Julia Kociuba, Agata Krawczyk, Natalia Pawełczak, Justyna Czechowicz

Software: Paweł Czechowicz, Mikołaj Antkiewicz, Szymon Kurciński, Julia Kurcińska

Check: Aleksandra Arczyńska-Antkiewicz, Maria Drozd, Paulina Łobaza, Gabriela Zając

Formal analysis: Martyna Kudła, Agata Krawczyk, Natalia Pawełczak, Paweł Czechowicz

Investigation: Julia Kociuba, Zuzanna Kruczek, Dorota Kołkowicz, Maria Drozd

Resources: Julia Kociuba, Mikołaj Antkiewicz, Paulina Łobaza, Gabriela Zając

Data curation: Aleksandra Arczyńska-Antkiewicz, Maria Drozd, Julia Kurcińska

Writing-rough preparation: Zuzanna Kruczek, Martyna Kudła, Agata Krawczyk, Natalia Pawełczak, Dorota Kołkowicz

Writing-review and editing: Julia Kociuba, Paweł Czechowicz, Justyna Czechowicz, Mikołaj Antkiewicz, Aleksandra Arczyńska-Antkiewicz, Paulina Łobaza

Visualization: Szymon Kurciński, Julia Kurcińska, Gabriela Zając, Maria Drozd

Supervision: Zuzanna Kruczek, Agata Krawczyk, Aleksandra Arczyńska-Antkiewicz

Project administration: Julia Kociuba

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