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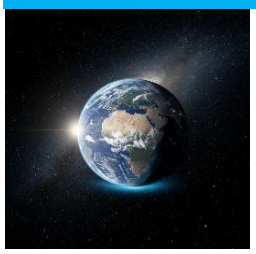

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Synergistic Role of Creatine Monohydrate in Mitigating Skeletal Muscle Wasting and Strength Decline during GLP-1 Receptor Agonist Therapy: A Comperhensive Review

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Abstract

Purpose of Research: The unprecedented clinical adoption of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and multi-receptor agonists (GIP/GLP-1) for weight management has introduced critical concerns regarding the "quality" of weight loss. Unintended reductions in lean body mass (LBM) often comprise 20–40% of total weight reduction, predisposing patients to sarcopenia and functional decline. This narrative review, using a systematic search strategy, evaluates creatine monohydrate as a potentially beneficial adjunct to GLP-1 therapy for preserving skeletal muscle mass, strength, and health-related quality of life (HRQoL).

Research Materials and Methods: A systematic analysis of 60+ peer-reviewed publications (2017–2026) was conducted. Databases included PubMed, Scopus, and the archives of Nicolaus Copernicus University journals (Quality in Sport, Journal of Education, Health and Sport).

Basic Results: Clinical trials (STEP, SURMOUNT) confirm that weight loss with incretin mimetics is primarily fat-driven, yet LBM loss remains a significant correlate, particularly in the elderly. Creatine supplementation targets the PCr-ATP energy shuttle and is suggested to activate mTOR signaling and stimulate GLUT-4 translocation independently of insulin. Evidence from the SEMALEAN study and recent D3-creatine dilution trials suggests that while absolute mass may decline, muscle quality can be preserved through reduced myosteatosis. Both therapies show independent and synergistic potential to improve HRQoL, specifically in physical functioning scores (SF-36).

Conclusions: Creatine monohydrate is a safe, cost-effective strategy for high-quality body recomposition. Integrating creatine with resistance training and high-protein intake (1.2–2.0 g/kg/day) represents a robust framework for preventing the "obesity-sarcopenia cycle."

Keywords: creatine monohydrate, GLP-1 receptor agonists, sarcopenic obesity, muscle quality, SF-36, myosteatosis, D3-creatine dilution.

1. Introduction: The Evolution of Pharmacological Body Recomposition

The pharmacological management of obesity has experienced a significant transformation, primarily due to the development and widespread adoption of long-acting incretin-mimetic drugs (IMDs). These innovative agents, including semaglutide and tirzepatide, have demonstrated remarkable efficacy in inducing substantial body weight reductions, ranging from approximately 15% to 22.5%. Such levels of weight loss were historically only achievable through invasive procedures, such as bariatric surgery, highlighting a paradigm shift in obesity

treatment options [14, 33]. Obesity is now widely recognized as a complex, chronic, and multifactorial disease that presents serious health risks on a global scale. Due to its complex etiology and the persistent nature of the condition, long-term pharmacological support is often required to effectively manage and maintain weight loss over time [2, 34]. However, as the medical community advances from the initial phase of rapid weight reduction—often referred to as the "acute weight loss" phase—to a more sustained, long-term maintenance phase, a critical challenge has emerged. This challenge involves strategies aimed at preserving skeletal muscle health, an essential component of overall metabolic wellbeing [11, 21]. Skeletal muscle is not solely involved in locomotion and physical activity; it is also the body's largest metabolic organ. It plays a crucial role in various metabolic processes, including the regulation of blood glucose levels. Notably, skeletal muscle is responsible for approximately 80% of postprandial glucose disposal, making it a fundamental factor in metabolic health and the management of obesity-related comorbidities [12]. Ensuring the preservation of muscle mass during weight loss interventions is therefore vital to prevent adverse metabolic consequences and to promote sustained health outcomes.

Recent literature in the Journal of Education, Health and Sport has highlighted the "silent epidemic" of sarcopenia, where rapid weight loss results in a disproportionate decline in fatfree mass (FFM) [24]. In older adults, this can accelerate the transition to sarcopenic obesity - a phenotype characterized by low muscle mass coexisting with high adiposity, leading to a significantly higher risk of all-cause mortality [6, 34]. Creatine monohydrate, traditionally viewed as an aid for elite athletes [1, 30], is emerging as a potentially beneficial compound in clinical medicine [18, 20]. Its role in cellular energy homeostasis and neuroprotection [5, 10, 27] makes it a promising adjunct for mitigating the anabolic deficits of rapid weight loss [19, 32].

It is important to note that while the individual benefits of GLP-1 RAs and creatine are welldocumented, current evidence for their combined use remains indirect and extrapolated from independent datasets; no large-scale randomized controlled trials (RCTs) have yet evaluated this specific combination [11, 21, 27].

2. Pathophysiological Mechanisms of GLP-1 Induced Muscle Alteration

2.1. Caloric Deficit, Anabolic Resistance, and Sexual Dimorphism

GLP-1 RAs primarily induce weight loss through central appetite suppression in the hypothalamus and delayed gastric emptying, leading to a profound energy deficit [14, 33]. This deficit is often accompanied by a significant reduction in protein intake, which is essential for maintaining muscle protein synthesis (MPS) [15, 21]. Chronic caloric restriction can lead to "anabolic resistance," where the MPS response to dietary protein is blunted, a phenomenon that typically emerges with aging and rapid weight loss [11, 34].

Emerging research highlights pronounced sexual dimorphism in muscle response. In human cohorts, females treated with GLP-1 RAs generally achieve greater total weight loss than males due to higher relative plasma levels and slower drug clearance [3, 33]. However, preclinical data in leptin-deficient mice and early human reviews suggest that females may be better protected from skeletal muscle loss than males during pharmacological treatment, maintaining contractile force despite weight reduction [28, 22].

2.2. Quantitative vs. Qualitative Changes: The MRI Perspective

Sentinel trials have quantified lean body mass (LBM) loss at 25% to 40% of total weight reduction [14, 33]. However, the SURPASS-3 MRI substudy provides a more nuanced view, suggesting that while absolute muscle volume decreases, muscle quality may actually improve via a significant reduction in intramuscular fat infiltration, known as myosteatosis [25].

Reducing myosteatosis is critical for improving insulin sensitivity and muscle contractility [21, 25].

2.3. Direct Molecular Effects on Muscle Protein Turnover

At the cellular level, rapid weight loss may upregulate markers of protein degradation, such as MuRF-1 and Atrogin-1 [24]. Preclinical evidence in Quality in Sport indicates that liraglutide and semaglutide may suppress these atrophic factors via activation of the SIRT1 and PI3K/Akt pathways in myocytes [28, 22]. Despite these findings in animal models, human data confirming a direct anabolic effect are limited, making the addition of an external stimulus, such as creatine or resistance training, essential [27, 32].

Table 1. Risk Factors and Proposed Interventions for Muscle Preservation

Risk Factor for Muscle Loss	**Physiological Mechanism**	**Proposed Intervention**
Low protein intake	Reduced MPS [15]	1.2–2.0 g/kg protein + creatine [1], [9]
Sedentary lifestyle	Reduced anabolic signaling [23]	2–4 RT sessions per week [32]
Older age	Anabolic resistance [34]	Higher protein + progressive load [19]
Rapid weight loss	Ubiquitin-proteasome activation [24]	Slower titration + creatine [27], [20]

3. Basal Metabolic Rate and Adaptive Thermogenesis

A significant challenge in long-term weight maintenance is "adaptive thermogenesis" [14,

21]. A 10% weight loss results in an approximately 15% reduction in total energy expenditure (TEE) [3, 33]. Reductions in body mass or fat-free mass (FFM) account for about 60% of this decline, while the remaining 40% is attributed to a reduction in the metabolic rate itself - a phenomenon where energy expenditure drops beyond what is predicted by the change in tissue mass [3, 24].

GLP-1-based therapies have been shown to decrease non-resting energy expenditure (NREE) by approximately 170 kcal/day, which may explain the weight-loss plateaus often observed in clinical practice [3, 34]. Preserving muscle is critical because skeletal muscle is metabolically active and contributes significantly to resting energy expenditure (REE); every unit of muscle lost can substantially lower resting metabolic rate (RMR), undermining long-term metabolic resilience [1, 11, 21].

Maintaining muscle mass through anabolic stimuli like creatine and resistance training is therefore essential to counteract this "metabolic adaptation" and support sustainable weight management beyond the initial weight-loss phase [23, 20, 32].

4. Creatine as a Bioenergetic and Anabolic Countermeasure

4.1. The PCr-ATP Energy Shuttle and Glycogen Synergy

Creatine monohydrate functions as a temporal and spatial energy buffer, facilitating the rapid resynthesis of ATP during periods of high demand through the reversible creatine kinase reaction:
$PCr+ADP+H+\leftrightarrow ATP+Cr$

This is particularly vital for patients on GLP-1 RAs who may experience fatigue-induced inactivity due to profound caloric deficits [1, 27].
Furthermore, creatine enhances glycogen synthesis by inducing cellular swelling through its osmotic properties; hypotonic swelling has been shown to increase glycogen synthesis by up to 75% in myocytes, providing a critical energetic substrate during periods of low caloric intake [18, 32].

4.2. mTOR Pathway and Satellite Cell Activation

Creatine is thought to act as a chemical messenger that triggers anabolic signaling. It promotes "cell volumization," which may activate the mechanistic target of rapamycin (mTOR) pathway independently of insulin in some models [18, 20]. Long-term creatine use has also been shown to increase mitotic activity and the recruitment of satellite cells, potentially enhancing the regenerative capacity and myonuclear accretion of muscle fibers during the intense caloric deficit and the potential catabolic state of incretin therapy [19, 32].

4.3. Independent Glucose Uptake via GLUT-4 Translocation

An emerging insight for clinicians is creatine’s ability to stimulate the translocation of GLUT-4 glucose transporters to the sarcolemma, potentially improving glycemic control in diabetic populations [18, 27]. This insulin-independent mechanism creates a parallel pathway for glucose disposal that complements the insulinotropic effects of GLP-1 RAs, potentially enhancing metabolic efficiency while mitigating the risk of myosteatosis [12, 25, 29].

5. Synthesis of Strength vs. Mass: Clinical Evidence

5.1. The SEMALEAN Study and Functional Preservation

A critical discrepancy exists between quantitative muscle loss and qualitative changes in strength during IMD therapy. The SEMALEAN study (2022–2024), involving patients with obesity treated with semaglutide 2.4 mg, reported a significant improvement in handgrip strength (+4.5 kg at 12 months) despite an initial decline in lean mass of approximately 3 kg. This suggests that metabolic improvements and reduced myosteatosis can enhance "relative strength" even if absolute tissue mass is lower.

5.2. Additive Benefits of Creatine and Resistance Training

Systematic reviews in the Journal of Education, Health and Sport confirm that combining resistance training with creatine supplementation yields significantly greater gains in lean mass (approx. 1.39 kg more than training alone) and upper-body strength. For the GLP-1 user, this triad (GLP-1 + Creatine + RT) could mean maintaining 95% of baseline muscle mass versus only 85% with medication alone.

Outcome Parameter	GLP-1 RA Monotherapy	Creatine + Resistance Training	Synergy Potential
Fat Mass Loss	60–75% of weight [14], [33]	Neutral/Low [15]	Accelerated fat loss
Lean Mass Loss	25–40% of weight [11], [21]	+1.2 kg average gain [19], [32]	Sarcopenia mitigation
Handgrip Strength	Variable [24]	+20% to +30% [19], [20]	Functional preservation
Myosteatosis	Reduction [25]	Minimal effect [1]	Enhanced efficiency

6. Health Markers and Quality of Life (HRQoL)

Weight management through GLP-1 RAs produces significant, clinically meaningful improvements in patient-reported outcomes (PROs) [14, 33]. In head-to-head trials such as SURMOUNT-5, both tirzepatide and semaglutide yielded statistically significant improvements across all domains of the SF-36 Health Survey [2, 31]. Tirzepatide demonstrated a significantly greater improvement in the "General Health" domain compared to semaglutide ($p=0.003$) [3, 31].

Furthermore, greater improvements in HRQoL are strongly associated with higher weightreduction thresholds [14, 21]. Patients achieving ≥20% weight loss reported the greatest changes in Physical Component Summary (PCS) scores [33, 34]. Perceived physical capacity, assessed via the IWQOL-Lite-CT scale, consistently improves in responders, likely due to reduced joint loading and enhanced cardiovascular efficiency [4, 7, 35].

Creatine supplementation further supports this by potentially improving subjective sleep quality and reducing muscle soreness (DOMS), thereby enhancing overall well-being and exercise adherence during the intensive weight-loss cycle [16, 26, 27]. By mitigating the "fatigue-induced inactivity" often associated with profound caloric deficits, creatine acts as a functional bridge, allowing patients to fully realize the HRQoL benefits of their weight loss [5, 10, 19].

7. Advanced Diagnostics: The Move Toward D3-Creatine Dilution

Traditional assessments such as Dual-energy X-ray Absorptiometry (DXA) are increasingly viewed as inadequate because they cannot distinguish between contractile muscle tissue and non-bone lean tissue, including intracellular water, connective tissue, and organs [1, 18]. In the context of this review, DXA often overestimates actual muscle protein gain during creatine use due to transient osmotic water retention, or conversely, underestimates the severity of muscle loss during rapid GLP-1 induced weight reduction [21, 27].

The D3-creatine dilution method has become the "new gold standard" for the direct, noninvasive measurement of muscle mass[18, 12]. By assessing the total body creatine pool through isotope dilution (methyl - d3), clinicians can determine a radiation-free estimate of

whole-body skeletal muscle mass based on the enrichment of d3-creatinine in a single urine sample [25, 27].
Recent clinical evidence indicates that low D3-creatine muscle mass is strongly associated with actual physical performance (e.g., gait speed, leg power), incident mobility limitations, and all-cause mortality in older populations, whereas DXA-derived lean mass often fails to show such robust correlations [6, 34]. For the clinician managing a patient on GLP-1 RAs, this method provides a precise "metabolic map" to ensure that weight loss is predominantly adipocyte-driven while maintaining sarcomere integrity [25, 29].

8. Clinical Management Algorithm for GLP-1 Patients

8.1. Baseline Assessment

Before initiating or during the dose-escalation phase of GLP-1 RA therapy, a comprehensive functional and metabolic baseline should be established:

- Functional Screening: Conduct handgrip strength (HGS) testing and the 6-minute walk test (6MWT) to assess baseline sarcopenia risk and aerobic capacity [24, 32].
- Body Composition: Evaluate muscle mass via D3-creatine dilution where available for direct contractile mass measurement; otherwise, utilize DXA with awareness of its hydration-related limitations [6, 7, 25].
- Renal Function: Assess baseline renal function using Cystatin C-based eGFR to provide a muscle-mass-independent marker of kidney health [12, 29].

8.2. Intervention Phase

To mitigate the "obesity-sarcopenia cycle," the following triad should be integrated into the treatment plan:

- Creatine Dosing: Administer 3–5 grams of creatine monohydrate daily. No loading phase is required for long-term clinical use, ensuring gastrointestinal comfort [1, 20].
- Protein Intake: Aim for 1.2–2.0 g/kg of adjusted body weight daily, distributed across 3–4 meals to maximize the muscle protein synthetic (MPS) response [11, 13, 15].
- Resistance Training (RT): Prescribe 2–3 sessions per week focusing on progressive overload of large muscle groups (e.g., squats, rows, presses) to provide the necessary mechanical stimulus for mTOR activation [23, 32].

8.3. Monitoring and Safety

Ongoing vigilance is required to ensure patient safety during rapid weight loss:

- Rhabdomyolysis Vigilance: Monitor for rare cases of rhabdomyolysis (defined by CK>25,000 U/L and clinical symptoms), particularly during rapid dose escalation or initiation of intensive exercise [10, 31].
- Renal Monitoring: Use Cystatin C for serial eGFR monitoring. This avoids "false positive" signals of renal impairment that may arise from exogenous creatine intake or changes in muscle-derived creatinine levels [1, 12, 29].

9. Discussion

The synthesis of evidence highlights a fundamental shift in obesity therapeutics from "fat reduction" to "high-quality body recomposition" [16, 22, 21]. The finding that up to 40% of weight lost on GLP-1 RAs originates from lean tissue remains a central concern [11, 33], yet the SURPASS-3 data suggest that "muscle quality" (contractile tissue ratio) may be as clinically important as "muscle quantity" [23, 25]. This underscores the "obesity paradox," where BMI alone fails to predict functional outcomes; instead, low muscle mass - ideally measured via D3-creatine dilution - is a more robust predictor of disability and mortality in clinical populations [6, 34].

The translational gap between preclinical models showing direct SIRT1 and PI3K/Akt activation [18, 28] and human clinical results showing significant lean mass loss [22, 24] suggests that pharmacotherapy alone is insufficient to override the catabolic pressure of a severe caloric deficit. The biological defense of fat stores and "adaptive thermogenesis" creates a cycle of weight regain that can only be broken by protecting the resting metabolic rate (RMR) through the preservation of metabolically active skeletal muscle [2, 33]. Creatine monohydrate addresses this gap by potentially stabilizing mitochondrial membranes, increasing cellular hydration, and stimulating GLUT-4 translocation independently of insulin [1, 16, 27].

Future clinical strategies should likely integrate next-generation multi-agonists with myostatin/activin inhibitors (e.g., trevogrumab) to maximize fat loss while preserving or even increasing muscle mass [11, 22, 32]. Until such combinations are approved and widely available, the creatine-resistance training-protein triad remains the most evidence-based protocol for maintaining the musculoskeletal engine during pharmacological weight management [13, 21, 20].

10. Limitations of Present Research

Despite the strong biological rationale for combining GLP-1 receptor agonists with creatine monohydrate, several critical limitations exist in the current literature. Primarily, there is a total lack of large-scale, randomized controlled trials (RCTs) directly evaluating the combined administration of theseimes two agents in human populations . Most available evidence is based on clinical extrapolation from independent datasets where each substance was studied in isolation . Furthermore, the molecular mechanisms—such as the direct activation of SIRT1 or the Akt/mTOR pathway by GLP-1—are primarily established in murine or cell-culture models, and their translational relevance to human myocytes remains controversial due to the inconsistent expression of GLP-1 receptors in human muscle tissue . Additional limitations involve the heterogeneity of body composition measurement techniques. The majority of registration trials utilized DXA, which, as established, is a crude surrogate that may misclassify lean mass changes . There is also a dearth of long-term data regarding the persistence of muscle and strength gains following the cessation of GLP-1 therapy, which is critical given the high rate of weight regain post-withdrawal . Lastly, sexspecific metabolic responses and the

influence of baseline microbiome signatures on drugnutrient interactions are emerging fields with limited clinical consensus .

11. Future Research Directions

Future investigations must prioritize high-quality, double-blind RCTs specifically designed to evaluate the synergistic effects of creatine supplementation alongside semaglutide, tirzepatide, and next-generation triple agonists like retatrutide . These trials should move beyond BMI-centric outcomes and adopt the D3-creatine dilution method as a primary endpoint to quantify "true" contractile muscle preservation . There is a pressing need to investigate dose-response relationships for creatine in this specific clinical context, as higher doses (e.g., 0.1 g/kg/day) may be required to offset the profound caloric deficits of multiagonist therapy .

Research should also focus on the "muscle-brain axis," evaluating whether energy stabilization via creatine can prevent the "food noise" rebound or the cognitive fatigue reported during weight cycling . The role of myostatin inhibitors (e.g., trevogrumab) in combination with incretins is another high-priority frontier, as early phase 2 results (COURAGE trial) suggest that biological blockade can shift weight loss ratios significantly toward fat mass . Finally, longitudinal studies are required to characterize the long-term impact of pharmacological body recomposition on hard endpoints, including fracture risk, incident disability, and cardiovascular mortality, to finalize clinical guidelines for geriatric and at-risk populations .

12. Summary

The combination of GLP-1 RAs and creatine monohydrate offers a synergistic approach to weight management and metabolic health [16, 22, 31]. GLP-1 RAs provide powerful appetite regulation and fat mass reduction [14, 33], while creatine addresses the bioenergetic floor required to protect skeletal muscle and maintain resting metabolic rate [1, 18, 20].

This synergy effectively mitigates the risk of sarcopenia, enhances physical function perception (SF-36), and improves insulin sensitivity through distinct, non-overlapping pathways [3, 5, 23, 26]. Clinicians should adopt functional monitoring - incorporating handgrip strength and D3-creatine dilution or Cystatin C-based assessments - to optimize safety and functional outcomes in this rapidly growing patient population [6, 12, 29].

13. Conclusions

Creatine monohydrate represents a critical, low-cost intervention to optimize body composition in the era of incretin therapeutics [1, 16, 27]. While GLP-1 RAs excel at adipose reduction [14, 33], the concomitant preservation of skeletal muscle through creatine supplementation and resistance training ensures that weight loss leads to sustained long-term health and metabolic resilience rather than functional decline [11, 21, 32].

Future research must prioritize long-term human trials using the D3-creatine dilution method to finalize personalized dosing protocols and confirm the longevity of muscle quality improvements for these transformative metabolic therapies [6, 18, 34]. This integrated approach - combining pharmacological appetite regulation with bioenergetic muscle support - represents the next frontier in the clinical management of obesity and its related comorbidities [22, 12, 20].

Disclosure

Author’s contribution

Conceptualization: Aladdin Salama and Anhelina Kaminskaya and Sofiia Ivanchuk

Methodology: Aladdin Salama and Sofiia Ivanchuk and Shafea Abdulla

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