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Heterogeneous Effects of Incretin-Based Therapies and SGLT2 Inhibitors on Skeletal Muscle Mass, Intramuscular Fat, and Functional Outcomes: A Systematic Review and Perspective Towards a Phenotype-Guided Framework

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Abstract

Background: The therapeutic landscape for type 2 diabetes (T2D) and obesity has shifted from a glucocentric paradigm to one focused on organ protection and weight management. While Glucagon- like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) are now cornerstones of care, concerns regarding "iatrogenic sarcopenia" have emerged. Current evaluations often rely on Dual-energy X-ray Absorptiometry (DXA), which fails to capture muscle quality. This study aims to synthesize evidence from advanced imaging trials to clarify how these drugs remodel skeletal muscle and to propose a phenotype-guided prescribing framework.

Methods: We conducted a systematic review following PRISMA 2020 guidelines, searching PubMed, Embase, and Cochrane Library up to January 2026. We prioritized randomized controlled trials (RCTs) utilizing Magnetic Resonance Imaging (MRI) proton density fat fraction (PDFF) or Computed Tomography (CT) radiodensity (Hounsfield Units, HU) to assess myosteatosis and muscle quality, alongside functional outcomes (e.g., gait speed).

Results: Analysis of landmark trials (SURPASS-3 MRI, STEP 1, SLIM LIVER) reveals distinct remodeling patterns. Incretin-based therapies (e.g., Tirzepatide, Semaglutide) induce significant weight loss and absolute lean mass reduction. However, Tirzepatide significantly reduced muscle fat infiltration (-0.36%, $p<0.0001$) beyond what weight loss alone predicts, indicating a "quality optimization" effect. Despite muscle volume loss, functional metrics (gait speed) were preserved or improved, attributed to an enhanced power-to-weight ratio. Conversely, SGLT2 inhibitors (e.g., Dapagliflozin, Empagliflozin) demonstrated a "muscle-sparing" profile. Dapagliflozin increased paraspinal muscle radiodensity (+1.61 HU, $p<0.01$) without mass loss. Empagliflozin rapidly improved gait speed (+0.08 m/s, $p<0.001$) in frail older adults, suggesting bioenergetic enhancement.

Conclusions: GLP-1 RAs and SGLT2 inhibitors exert heterogeneous effects on the musculo-adipose unit. Incretins act as "Quality Optimizers" via deep lipid clearance, while SGLT2 inhibitors act as "Mass Preservers" and bioenergetic enhancers. We propose a "Cardiogeriatric Vulnerability Phenotype" framework to guide precision prescribing, ensuring metabolic benefits translate to long-term functional independence.

Keywords: Skeletal muscle quality; Myosteatosis; GLP-1 receptor agonists; SGLT2 inhibitors; Sarcopenia; Phenotype-guided therapy

Introduction

The Paradigm Shift: From Glycemic Control to Organ Protection

The management of metabolic diseases has undergone a paradigm shift over the last decade. Following the mandate for cardiovascular outcome trials (CVOTs), the clinical focus has moved from merely lowering Hemoglobin A1c (HbA1c) to a comprehensive strategy emphasizing organ protection— specifically reducing cardiovascular mortality, preventing heart failure, and preserving renal function [1]. In this era, Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) have emerged as disease-modifying therapies. Furthermore, the advent of dual GIP/GLP-1 agonists (e.g., Tirzepatide) has enabled weight reduction magnitudes of 15-20%, levels previously attainable only via bariatric surgery [2].

The Challenge of Iatrogenic Sarcopenia

However, profound pharmacologic weight loss raises critical questions regarding body composition. Physiologically, approximately 25% of weight lost during caloric restriction comes from lean body mass (LBM), including skeletal muscle [3]. In vulnerable populations, such as the elderly or those with "sarcopenic obesity," excessive muscle loss may precipitate frailty, falls, and functional decline, a phenomenon termed "iatrogenic sarcopenia" [4]. Distinguishing between pathological muscle wasting and physiological adaptation to reduced body mass is therefore paramount.

Beyond DXA: The Necessity of Assessing Muscle Quality

Traditional assessment via Dual-energy X-ray Absorptiometry (DXA) is limited by its inability to distinguish contractile muscle from myosteatosis (intramuscular fat infiltration) and its susceptibility to hydration errors—a significant confounder with diuretic SGLT2 inhibitors [5]. Emerging evidence suggests that "muscle quality," defined by low fat infiltration and high mitochondrial efficiency, is a superior predictor of functional outcomes than muscle mass alone [6]. This review synthesizes data from advanced imaging studies (MRI, CT) to contrast the musculoskeletal effects of incretin therapies versus SGLT2 inhibitors.

Methods

This systematic review was conducted in accordance with PRISMA 2020 guidelines [7]. We searched PubMed/MEDLINE, Embase, and Cochrane Library databases for English-language studies published through January 10, 2026.

- ***Inclusion Criteria:*** RCTs or prospective studies involving adults with T2D, obesity, or metabolic dysfunction-associated steatotic liver disease (MASLD); interventions using GLP-1 RAs, Dual Agonists, or SGLT2i; outcomes reporting objective body composition via DXA, MRI (PDFF), or CT (HU), and/or physical function (gait speed, grip strength).
- ***Data Extraction:*** Primary endpoints were changes in myosteatosis (muscle fat) and lean mass. Secondary endpoints included functional changes. Data from landmark trials (STEP 1, SURPASS-3 MRI, SLIM LIVER) and mechanistic studies (Sugiyama et al., Mone et al.) were prioritized for quantitative synthesis.

Results: Incretin-Based Therapies (GLP-1 RA / Dual Agonists)

Tirzepatide and the "Quality Optimization" Effect

The SURPASS-3 MRI substudy provided granular data on the effects of the dual GIP/GLP-1 agonist Tirzepatide.

- ***Myosteatosis Clearance:*** Over 52 weeks, Tirzepatide treatment resulted in a significant reduction in muscle fat infiltration (MFI) of ***-0.36 percentage points*** (95% CI -0.48 to -0.25, $p < 0.0001$) [8]. Crucially, regression analysis against a UK Biobank reference population showed this reduction was significantly greater than that predicted by weight loss alone, suggesting a drug-specific mechanism—likely improved lipid partitioning preventing "spillover" into ectopic sites [8].
- ***Adaptive Mass Reduction:*** While absolute muscle volume decreased (-0.64 L), Z-score analysis confirmed this loss was proportional to total body weight reduction, supporting the "Adaptive Response" hypothesis rather than pathological wasting [8].

Semaglutide: Mass Loss vs. Functional Preservation

- ***Body Composition (STEP 1):*** In the STEP 1 trial, Semaglutide 2.4 mg resulted in a ~15% total body weight loss. DXA analysis indicated that lean mass accounted for approximately ***40%*** of the total weight lost (approx. -5.44 kg lean mass vs -8.4 kg fat mass) [3]. Despite this, the *proportion* of lean mass relative to total body weight increased by 3.0 percentage points due to the massive reduction in fat mass [3].
- ***Functional Outcomes (SLIM LIVER):*** In the SLIM LIVER study involving patients with HIV and MASLD, Semaglutide 1.0 mg led to a significant ***9.3% decrease*** in psoas muscle volume ($p < 0.001$) [9]. However, this did not translate to functional decline. Conversely, the prevalence of slow gait speed (<1 m/s) significantly decreased from 63% to ***46%*** ($p = 0.029$), and sit-to-stand performance showed a trend toward improvement [9].

Results: SGLT2 Inhibitors

Dapagliflozin and Muscle Sparing

SGLT2 inhibitors induce a unique catabolic state mimicking fasting, promoting lipolysis while preserving protein.

- ***Radiodensity Improvements:*** In a CT-based study by Sugiyama et al., Dapagliflozin 5 mg significantly increased the radiodensity of paraspinal muscles by ***+1.61 HU*** ($p < 0.01$) over 24 weeks [10]. Higher HU values reflect reduced intramuscular fat and increased tissue density.
- ***Mass Preservation:*** Unlike GLP-1 RAs, Dapagliflozin did not result in a statistically significant reduction in Skeletal Muscle Index (SMI) or Psoas Muscle Index (PMI), confirming a "muscle- sparing" phenotype [10].

Empagliflozin and Bioenergetics in the Frail

Mone et al. investigated Empagliflozin in frail elderly patients with T2D and heart failure with preserved ejection fraction (HFpEF).

- ***Functional Gains:*** After just 1 month, patients treated with Empagliflozin showed a clinically meaningful increase in 5-meter gait speed of ***+0.08 m/s*** ($p < 0.001$) compared to active comparators [11].
- ***Cognitive-Motor Link:*** Montreal Cognitive Assessment (MoCA) scores improved by ***+2.45 points*** ($p < 0.001$) [11]. Given the short timeframe, these benefits are attributed to improved mitochondrial bioenergetics and ketone body utilization rather than hypertrophy.

Discussion: Comparative Physiology

Mechanisms of Action

The divergence in musculoskeletal outcomes stems from distinct mechanisms. GLP-1 RAs drive potent weight loss via central appetite suppression, leading to mechanical unloading and an improved ***Power-to-Weight Ratio***. The loss of muscle mass is largely an adaptive downregulation to a lighter load [9]. SGLT2 inhibitors, by inducing glycosuria, shift metabolism toward fatty acid oxidation

and ketogenesis, enhancing mitochondrial efficiency (bioenergetics) and reducing oxidative stress, which preserves muscle quality and mass [12].

Comparative Framework

Table 1 summarizes the distinct profiles of these two classes.

Feature	*Incretin Therapies (GLP-1 Ras / Dual Agonists)*	*SGLT2 Inhibitors (SGLT2i)*
Primary Driver	Central appetite suppression; delayed gastric emptying.	Glycosuria (Caloric loss); metabolic switching (fasting mimicry).
Weight Loss	High Magnitude (10-20%+)	Moderate Magnitude (2-4%)
Muscle Quantity	**Absolute Reduction.** Generally proportional to weight loss (Adaptive Response) [8].	**Preservation.** Muscle-sparing effect; stable Skeletal Muscle Index [10].
Muscle Quality	**Optimized via Lipid Clearance.** Significant reduction in MRI- PDFF (-0.36%) [8].	**Optimized via Density Increase.** Significant increase in CT Radiodensity (+1.61 HU) [10].
Functional Outcome	**Maintained or Improved.** Driven by improved *Power-to- Weight Ratio* despite mass loss [9].	**Significantly Improved.** Driven by *Bioenergetics* & mitochondrial efficiency [11].
Key Mechanism	Lipid Partitioning & Mechanical Unloading.	Ketogenesis & Oxidative Stress Reduction.

Table 1: Comparative Musculo-Adipose Remodeling Profiles of Incretin Therapies vs. SGLT2 Inhibitors.

Clinical Implications: A Phenotype-Guided Framework

We propose a clinical decision framework moving beyond BMI to "Musculo-Adipose Phenotypes" (Table 2).

Clinical Phenotype	*Patient Characteristics*	*Recommended Therapy*	*Clinical Rationale*
The "Robust" Obese	• BMI > 35 kg/m^2 • High baseline muscle mass • Severe visceral adiposity • Metabolic Syndrome	**GLP-1 RA / Dual Agonist** *(e.g., Semaglutide, Tirzepatide)*	Patient has sufficient muscle reserve to tolerate adaptive mass loss. Priority is deep clearance of visceral/ectopic fat. Weight loss improves biomechanics (Power-to-Weight ratio).
The Sarcopenic / Frail	• Age > 65 or Frailty • BMI < 32 kg/m^2 or "Skinny Fat" • Low gait speed (< 0.8 m/s) • History of falls	**SGLT2 Inhibitor** *(e.g., Dapagliflozin, Empagliflozin)*	Priority is "Do No Harm" to muscle. SGLT2i preserves mass and enhances mitochondrial function (gait speed). If GLP-1 required, use low dose + resistance training.

The Cardiogeriatric	• Heart Failure (HFpEF) • Cognitive impairment • High cardiovascular risk • Functional limitation	**SGLT2 Inhibitor**	First-line for HFpEF and bioenergetic support.[11] GLP-1 RA may be added for CV risk reduction but requires careful monitoring of functional status.

Table 2: Phenotype-Guided Prescribing Framework for Metabolic Therapies.

Conclusion

Contemporary metabolic drugs exert heterogeneous effects on skeletal muscle. ***Tirzepatide and Semaglutide*** act as "Quality Optimizers," stripping away ectopic fat to improve muscle quality and biomechanical efficiency, albeit with adaptive mass loss. ***SGLT2 inhibitors*** act as "Mass Preservers" and bioenergetic enhancers, making them ideal for frail or sarcopenic populations. Clinicians should adopt a phenotype-guided strategy, integrating functional assessments (e.g., gait speed) and advanced imaging concepts to personalize care and preserve long-term independence.

References

1. American Diabetes Association Professional Practice Committee. "9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2022". Diabetes Care 45.Supplement_1 (2022): S125-S143.
2. Jastreboff AM., et al. "Tirzepatide Once Weekly for the Treatment of Obesity". N Engl J Med 387.3 (2022): 205-216.
3. Wilding JPH., et al. "Impact of Semaglutide on Body Composition in Adults with Overweight or Obesity: Exploratory Analysis of the STEP 1 Study". J Endocr Soc 5.Suppl 1 (2021): A16-A17.
4. Sarcopenic Obesity Global Leadership Initiative (SOGLI). Definition and Diagnostic Criteria for Sarcopenic Obesity. Clin Nutr 41.4 (2022): 990-1002.
5. Heymsfield SB., et al. "Weight Loss Composition is One-Fourth Fat-Free Mass: A Critical Review and Critique of This Widely Cited Rule". Obes Rev 15.4 (2014): 310-321.
6. Correa-de-Araujo R., et al. "Myosteatosis in the Context of Skeletal Muscle Function Deficit: An Interdisciplinary Workshop at the National Institute on Aging". Front Physiol 11 (2020): 963.
7. Page MJ., et al. "The PRISMA 2020 statement: an updated guideline for reporting systematic reviews". BMJ 372 (2021): n71.
8. Sattar N., et al. "Tirzepatide and muscle composition changes in people with type 2 diabetes (SURPASS-3 MRI): a post-hoc analysis of a randomised, open-label, parallel-group, phase 3 trial". Lancet Diabetes Endocrinol 10.10 (2022): 707-715.
9. Ditzenberger GL., et al. "Effects of Semaglutide on Muscle Structure and Function in the SLIM LIVER Study". Clin Infect Dis 80.2 (2024): 389-396.
10. Sugiyama S., et al. "Dapagliflozin Reduces Fat Mass without Affecting Muscle Mass in Type 2 Diabetes". J Atheroscler Thromb 25.6 (2018): 467-476.
11. Mone P., et al. "Empagliflozin Improves Cognitive Impairment in Frail Older Adults with Type 2 Diabetes and Heart Failure with Preserved Ejection Fraction". Diabetes Care 45.5 (2022): 1247-1251.
12. Ferrannini E, Mark M and Mayoux E. "CV Protection in the EMPA-REG OUTCOME Trial: A "Thrifty Substrate" Hypothesis". Diabetes Care 39.7 (2016): 1108-1114.