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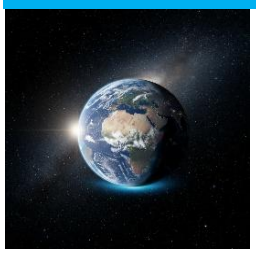

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Do SGLT2 Inhibitors Affect Skeletal Muscle Mass and Strength? A Systematic Review of Body Composition and Functional Outcomes

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Abstract

Background.
Sodium–glucose cotransporter-2 inhibitors (SGLT2i) are widely used in the treatment of type 2 diabetes mellitus, chronic kidney disease, and heart failure. Although these agents promote weight loss and improve cardiometabolic outcomes, concerns have emerged regarding potential reductions in skeletal muscle mass and their impact on physical function.
Aim.
To review current evidence on the effects of SGLT2 inhibitors on skeletal muscle mass, muscle strength, and functional outcomes.
Material and methods.
A systematic narrative review of English-language studies published between 2020 and 2026 was conducted. Randomized controlled trials, observational studies, and meta-analyses evaluating body composition and functional performance outcomes during SGLT2 inhibitor therapy were included.
Results.
SGLT2 inhibitors consistently reduced body weight primarily through fat mass loss, while reductions in lean mass were generally small. Skeletal muscle mass and handgrip strength were largely preserved in middle-aged adults, whereas greater variability was observed in older individuals and patients with chronic kidney disease. Evidence suggests that physical activity and adequate nutrition may mitigate potential muscle loss.
Conclusions.
SGLT2 inhibitors promote favorable body recomposition with predominantly fat mass reduction and minimal effects on muscle function in most patients. Monitoring muscle health and supporting lifestyle interventions may be beneficial in vulnerable populations.
Key words: SGLT2 inhibitors, skeletal muscle, lean mass, sarcopenia, handgrip strength, body composition, functional outcomes.

1. Introduction

Sodium–glucose cotransporter-2 inhibitors (SGLT2i) have fundamentally transformed the therapeutic landscape of cardiometabolic medicine over the past decade. Initially introduced as glucose-lowering agents for the management of type 2 diabetes mellitus (T2DM), this drug class has demonstrated robust and reproducible benefits on hard clinical endpoints, including reductions in hospitalization for heart failure, slowing of chronic kidney disease (CKD) progression, and decreases in cardiovascular and all-cause mortality. These benefits extend to

patients both with and without diabetes, leading to rapid expansion of SGLT2i indications across cardiology, nephrology, and internal medicine guidelines. Consequently, SGLT2 inhibitors are increasingly prescribed to older adults and patients with advanced multimorbidity, populations in whom preservation of physical function and muscle health is of paramount importance.

The pleiotropic mechanisms underlying the clinical benefits of SGLT2 inhibitors include osmotic diuresis and natriuresis, reduction of preload and afterload, improvement of myocardial energetics, attenuation of intraglomerular hypertension, modulation of inflammatory and oxidative stress pathways, and favorable shifts in systemic metabolism. A consistent metabolic effect observed across clinical trials and real-world studies is modest but sustained weight loss, typically ranging from 2 to 4 kg over 6–12 months of therapy. This weight reduction is primarily driven by urinary glucose excretion, which results in a chronic negative energy balance of approximately 200–300 kcal per day. In addition, mild diuretic effects contribute to early changes in body weight during the initial weeks of treatment.

While weight reduction is generally desirable in patients with cardiometabolic disease, the clinical significance of weight loss depends critically on its composition. Preferential loss of fat mass—particularly visceral and ectopic adipose tissue—is associated with improvements in insulin sensitivity, lipid metabolism, blood pressure regulation, inflammatory burden, and cardiometabolic risk. In contrast, loss of skeletal muscle mass and function is associated with adverse outcomes including frailty, falls, disability, reduced aerobic capacity, impaired glucose disposal, and increased mortality. The concept of sarcopenia, defined by low muscle mass accompanied by reduced muscle strength or physical performance, has gained increasing recognition as a major determinant of prognosis in populations commonly treated with SGLT2 inhibitors, including individuals with T2DM, CKD, and heart failure.

Importantly, patients with cardiometabolic disease often exhibit baseline impairments in skeletal muscle health even before initiation of pharmacological therapy. Insulin resistance promotes anabolic resistance in skeletal muscle, reducing the capacity of muscle tissue to respond to dietary protein and exercise stimuli. Chronic low-grade inflammation, oxidative stress, mitochondrial dysfunction, and reduced physical activity further contribute to impaired muscle protein synthesis and increased proteolysis. In patients with CKD, additional catabolic drivers include metabolic acidosis, accumulation of uremic toxins, endocrine disturbances (including alterations in vitamin D and testosterone signaling), and protein–energy wasting.

Heart failure is similarly associated with skeletal muscle atrophy, reduced oxidative capacity, and shifts in muscle fiber composition that contribute to exercise intolerance and reduced quality of life. These baseline vulnerabilities raise concerns that pharmacologically induced negative energy balance, such as that produced by SGLT2 inhibitors, may exacerbate pre-existing tendencies toward muscle loss in susceptible individuals.

Early clinical trials of SGLT2 inhibitors focused primarily on glycemic outcomes, cardiovascular events, renal endpoints, and overall changes in body weight. Only subsequently did investigators begin to explore the composition of weight loss using techniques such as dual-energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA). These studies have produced heterogeneous results, with some reporting small but measurable reductions in lean mass and others suggesting that fat mass loss predominates with relative preservation of skeletal muscle [1–4]. Meta-analyses indicate that although lean mass may decrease to a limited extent, the proportion of lean tissue lost relative to total weight loss is generally modest and smaller than that observed with some other weight-reducing interventions [1–4,7,8]. Nevertheless, even small absolute losses of muscle mass may be clinically meaningful in older adults and patients with advanced comorbidity, in whom baseline muscle reserves are limited.

Beyond structural measures of body composition, functional outcomes such as muscle strength, gait speed, balance, and risk of falls are of critical importance from a clinical and patient-centered perspective. Muscle function is often more strongly associated with morbidity and mortality than muscle mass alone. However, functional endpoints have been inconsistently reported in clinical trials of SGLT2 inhibitors, and many studies were not powered or designed to detect subtle changes in physical performance. As SGLT2 inhibitors are increasingly prescribed to frail older adults and patients with CKD or heart failure, the paucity of high-quality data on functional outcomes represents a significant knowledge gap.

Another important consideration is the role of modifying factors that may influence the impact of SGLT2 inhibitors on skeletal muscle health. Nutritional status, particularly protein intake, appears to modulate lean mass responses to pharmacologically induced weight loss. Similarly, engagement in resistance exercise and overall physical activity is a key determinant of muscle protein synthesis and functional capacity. Emerging interventional studies suggest that combining SGLT2 inhibitors with structured exercise programs and targeted nutritional support may mitigate potential lean mass loss and preserve muscle function in vulnerable populations

[27]. These findings highlight the importance of viewing pharmacological therapy within a broader framework of lifestyle and rehabilitation strategies.

Given the expanding use of SGLT2 inhibitors across diverse clinical populations and the growing emphasis on preserving functional capacity and healthy aging, a comprehensive synthesis of their effects on skeletal muscle mass, muscle strength, and functional outcomes is timely and clinically relevant. Clarifying the magnitude and clinical significance of muscle-related effects, identifying populations at risk of adverse outcomes, and highlighting potential mitigating strategies may inform individualized treatment decisions and optimize long-term patient outcomes.

Research Objective.

To systematically synthesize contemporary evidence on the effects of SGLT2 inhibitors on skeletal muscle mass, muscle strength, and functional outcomes in adults.

Research Problems.

1. Do SGLT2 inhibitors cause clinically meaningful loss of skeletal muscle mass?
2. Are muscle strength and physical performance adversely affected?
3. Which patient populations are at highest risk of muscle-related adverse outcomes?
4. Which co-interventions may mitigate potential risks to skeletal muscle health?

Research Hypotheses.

H1: SGLT2 inhibitors preferentially reduce fat mass relative to lean mass.

H2: Muscle strength and functional outcomes remain largely preserved in non-frail adults.

H3: Older adults and patients with CKD or frailty exhibit greater vulnerability to muscle loss and functional decline.

2. Research materials and methods

2.1. Study design and protocol

This study was conducted as a systematic narrative review designed to synthesize contemporary evidence on the effects of sodium–glucose cotransporter-2 inhibitors (SGLT2i) on skeletal muscle mass, muscle strength, and functional outcomes in adults. The review methodology was informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework to ensure transparent identification, screening, eligibility assessment, and inclusion of relevant studies. Given the heterogeneity of study designs, populations,

outcome definitions, and measurement techniques, a formal quantitative meta-analysis was not undertaken. Instead, a structured narrative synthesis was applied to integrate findings across randomized controlled trials (RCTs), prospective observational studies, and systematic reviews/meta-analyses [1–31].

A review protocol was developed a priori to define research questions, eligibility criteria, outcomes of interest, and data extraction variables. The protocol specified skeletal muscle-related endpoints as primary outcomes and functional performance measures as key secondary outcomes. The review focused on literature published between January 2020 and January 2026 to reflect contemporary clinical practice and the expanding indications of SGLT2 inhibitors.

2.2. Participants and populations of interest

The population of interest comprised adult participants (≥18 years) treated with SGLT2 inhibitors for T2DM, CKD, HF, or obesity-related indications. Studies enrolling both sexes and diverse ethnic groups were included. No restrictions were applied with respect to baseline body mass index (BMI), glycemic control, or disease duration, acknowledging that baseline metabolic status and adiposity may modify responses in body composition and muscle function. Particular attention was paid to studies enrolling populations at increased risk of sarcopenia or functional decline, including:

- older adults (≥65 years),
- patients with CKD (stages 1–5, including those with albuminuria),
- patients with HF,
- individuals with baseline low muscle mass, low muscle strength, or frailty.

Studies conducted in community-dwelling populations as well as in specialized clinical settings (diabetology, nephrology, cardiology clinics) were eligible.

2.3. Eligibility criteria

Inclusion criteria:

1. Original research articles (RCTs or prospective observational studies) or systematic reviews/meta-analyses.
2. Adult human participants receiving SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin, ipragliflozin, luseogliflozin).
3. Reporting at least one skeletal muscle-related outcome, including:

- body composition (DXA- or BIA-derived lean mass, appendicular lean mass, skeletal muscle index),
- muscle strength (e.g., handgrip strength),
- functional outcomes (gait speed, Short Physical Performance Battery, chair-stand test),
- clinical endpoints related to muscle health (falls, sarcopenia diagnosis).

4. English-language publications from 2020 to 2026.

Exclusion criteria:

1. Animal or in vitro studies.
2. Cross-sectional studies without longitudinal follow-up.
3. Case reports or small case series (<10 participants).
4. Studies without any body composition or functional outcome data.
5. Conference abstracts without full-text publication.

2.4. Information sources and search strategy

A comprehensive literature search was conducted in PubMed/Medline and PubMed Central (PMC), supplemented by manual searches of major publisher platforms (e.g., Frontiers, MDPI, Wiley, Elsevier). Search terms were combined using Boolean operators and included:

"sodium-glucose cotransporter 2 inhibitor" OR "SGLT2 inhibitor" OR "empagliflozin" OR "dapagliflozin" OR "canagliflozin" OR "ipragliflozin" OR "luseogliflozin"

AND

"skeletal muscle" OR "lean mass" OR "body composition" OR "appendicular lean mass" OR "muscle strength" OR "handgrip strength" OR "sarcopenia" OR "physical performance" OR "falls".

Reference lists of eligible systematic reviews and key original studies were manually screened to identify additional relevant publications. The final set of included sources comprised 31 high-quality studies and reviews [1–31].

2.5. Study selection process

Two-stage screening was applied. In the first stage, titles and abstracts were screened for relevance to SGLT2 inhibitors and muscle-related outcomes. In the second stage, full texts of potentially eligible studies were assessed against predefined inclusion and exclusion criteria. Studies meeting all eligibility criteria were included in the final synthesis. Discrepancies in study eligibility were resolved by consensus after full-text review.

A PRISMA-style narrative workflow was used to structure the selection process (identification → screening → eligibility → inclusion). Although numerical flow counts are not reported here, the final corpus of evidence reflects contemporary, peer-reviewed studies addressing body composition and/or functional outcomes associated with SGLT2i therapy [1–31].

2.6. Data extraction

Data were extracted using a standardized template to ensure consistency across studies. Extracted variables included:

- study design (RCT, prospective cohort, systematic review/meta-analysis),
- sample size and population characteristics (age, sex distribution, disease phenotype),
- SGLT2 inhibitor agent and dose,
- duration of follow-up,
- body composition assessment method (DXA vs BIA),
- changes in total lean mass, appendicular lean mass, skeletal muscle index, and fat mass,
- muscle strength outcomes (handgrip strength),
- functional performance measures (gait speed, SPPB, chair-stand test),
- reported adverse events related to muscle function (falls, sarcopenia classification),
- key conclusions and limitations reported by the authors.

2.7. Risk of bias and quality assessment

The methodological quality of RCTs was assessed qualitatively with reference to standard domains of bias, including randomization procedures, allocation concealment, blinding, completeness of outcome data, and selective reporting. Observational studies were appraised for risk of confounding, selection bias, and measurement bias. Systematic reviews and meta-

analyses were assessed for comprehensiveness of search strategy, transparency of inclusion criteria, and consistency of findings.

Overall, the quality of evidence was moderate to high for body composition outcomes derived from RCTs and meta-analyses [1–4,7,8], while functional outcomes were supported by fewer high-quality studies, limiting the certainty of conclusions regarding muscle performance.

2.8. Data synthesis and analytical approach

Due to heterogeneity in study populations, intervention duration, outcome definitions, and measurement techniques, a narrative synthesis approach was adopted. Findings were organized thematically according to:

- body composition outcomes (fat mass vs lean mass),
- skeletal muscle mass changes in different populations (middle-aged adults, elderly, CKD),
- muscle strength and functional performance,
- modifying factors (age, frailty, nutritional status, physical activity),
- effects of co-interventions (exercise, protein supplementation).

Where available, pooled estimates from meta-analyses were interpreted descriptively. Consistency and direction of effects were emphasized over statistical significance alone, in line with contemporary recommendations for evidence synthesis in heterogeneous clinical domains.

2.9. Use of AI tools

Artificial intelligence tools were used exclusively to assist with linguistic refinement and structural organization of the manuscript. All stages of study selection, data extraction, evidence synthesis, and interpretation were performed by the author. The AI tools did not influence the inclusion of studies, assessment of evidence quality, or formulation of clinical conclusions.

3. Research results

3.1. Effects on body composition: magnitude, pattern, and consistency of change (fat mass versus lean mass)

Across contemporary systematic reviews and meta-analyses, sodium–glucose cotransporter-2 inhibitors (SGLT2i) consistently produced statistically significant reductions in body weight, with the majority of weight loss attributable to decreases in fat mass rather than lean mass [1–4,7,8]. Mean reductions in body weight ranged from approximately 2 to 4 kg during 24–52

weeks of therapy, although variability across populations and study designs was observed. Fat mass reduction represented the dominant component of weight change, commonly accounting for more than half of total weight loss.

Interpretation of lean mass changes requires consideration of body composition physiology. Lean mass measurements include skeletal muscle, body water, connective tissue, and organ mass; therefore, reductions in measured lean mass do not necessarily correspond to proportional loss of contractile skeletal muscle tissue. Early reductions may reflect fluid redistribution associated with osmotic diuresis rather than structural muscle loss. This interpretation aligns with exercise physiology findings demonstrating that body composition adaptations depend on metabolic and mechanical stimuli rather than absolute weight change alone [31].

Meta-analytic evidence indicates that lean mass reductions associated with SGLT2 inhibitor therapy are generally modest, frequently below 1 kg, and proportionally smaller than fat mass reductions [1–4,7,8]. Such patterns suggest favorable body recomposition rather than pathological muscle wasting. Improvements in metabolic efficiency and reductions in visceral adiposity may contribute to improved functional capacity despite minor quantitative lean mass changes.

Studies employing dual-energy X-ray absorptiometry (DXA) demonstrated relatively stable appendicular lean mass, suggesting preservation of skeletal muscle compartments [18]. In contrast, bioelectrical impedance analysis (BIA), which is sensitive to hydration shifts, sometimes indicated larger early lean mass reductions. These discrepancies support the hypothesis that part of the observed lean mass decline represents transient fluid changes.

Real-world longitudinal studies further demonstrated improvements in skeletal muscle mass-to-fat mass ratio during prolonged SGLT2 inhibitor therapy, indicating preferential adipose tissue reduction [10]. From a functional standpoint, increases in relative muscle proportion are associated with improved strength performance and movement efficiency, findings consistent with training studies demonstrating that improved body composition correlates with enhanced muscular performance outcomes [31].

Comparative trials reinforced these conclusions. Dapagliflozin compared with sulfonylureas resulted in weight loss driven primarily by fat mass reduction, whereas comparator therapies promoted adiposity gain. Lean mass remained relatively preserved in SGLT2 inhibitor groups, highlighting mechanistic differences between metabolic therapies [17].

3.2. Skeletal muscle mass trajectories across clinical populations

3.2.1. Middle-aged adults with type 2 diabetes mellitus

In middle-aged adults with T2DM, prospective trials consistently demonstrated preservation of skeletal muscle mass during SGLT2 inhibitor therapy [15–17]. Absolute lean mass changes were small and rarely reached thresholds associated with sarcopenia development. Improved glycemic control and reduced visceral fat may enhance insulin sensitivity and indirectly support skeletal muscle metabolism.

Evidence from exercise intervention studies shows that improvements in body composition are closely linked with maintenance or enhancement of muscular strength when metabolic health improves [31]. These findings support the interpretation that SGLT2-induced fat loss may coexist with preserved functional muscle capacity.

3.2.2. Older adults

Studies focusing on elderly populations revealed greater variability in muscle mass responses [11,12]. While average reductions remained small, interindividual differences were substantial. Older individuals with lower physical activity or reduced protein intake appeared more susceptible to lean mass decline. Age-related anabolic resistance likely contributes to this variability, reducing the efficiency of muscle protein synthesis under conditions of energy deficit.

Exercise science literature indicates that structured physical activity can counteract age-related muscle loss and improve strength even when body weight decreases [31], suggesting that lifestyle factors strongly influence outcomes observed during pharmacological therapy.

3.2.3. Chronic kidney disease populations

Patients with CKD demonstrated more heterogeneous responses [13]. Small decreases in skeletal muscle mass were reported in some cohorts, accompanied by inconsistent strength changes. The catabolic environment characteristic of CKD—including inflammation, metabolic acidosis, and hormonal alterations—may amplify susceptibility to muscle loss.

Evidence from combined training programs demonstrates that mechanical loading remains a critical determinant of muscle preservation despite metabolic stressors [31]. These findings imply that exercise interventions may be particularly beneficial when SGLT2 inhibitors are used in CKD populations.

3.2.4. Heart failure populations

Direct skeletal muscle outcome data in heart failure cohorts remain limited. However, given the high prevalence of muscle wasting and exercise intolerance in HF, extrapolation from elderly

and CKD data suggests potential vulnerability. Future trials incorporating standardized muscle strength and functional performance assessments are needed.

3.3. Muscle strength and functional performance outcomes

3.3.1. Handgrip strength

Handgrip strength was the most frequently reported functional outcome and remained largely stable across studies [13,14]. The absence of significant strength decline despite small lean mass reductions supports the concept that muscle function depends not only on mass but also on neuromuscular efficiency and muscle quality.

Exercise studies demonstrate that improvements in body composition can enhance strength performance even without substantial increases in muscle mass [31], providing a physiological explanation for preserved functional outcomes observed during SGLT2 inhibitor therapy.

3.3.2. Functional performance measures

Evidence regarding gait speed, Short Physical Performance Battery (SPPB), and chair-stand performance was limited but generally neutral. No consistent deterioration in functional performance was observed among non-frail adults receiving SGLT2 inhibitors.

3.3.3. Falls and clinical outcomes

Observational analyses suggested possible associations between SGLT2 inhibitor therapy and falls in older adults [28]. However, confounding factors such as neuropathy, comorbid disease burden, and polypharmacy likely contribute to these findings. Current evidence does not establish causality.

3.3.4. Sarcopenia diagnosis

Few studies applied standardized sarcopenia criteria. Available observational data suggested possible risk signals in vulnerable populations [29], although inconsistent diagnostic approaches limit interpretation.

3.4. Time course of body composition adaptations

Early reductions in lean mass during initial treatment phases likely reflect fluid redistribution and glycogen depletion rather than structural muscle loss. Over longer follow-up, fat mass reduction predominates and lean mass stabilizes. Similar temporal patterns are observed in training-induced body recomposition, where metabolic adaptation initially alters hydration and energy stores before structural adaptations occur [31].

3.5. Modifying factors influencing outcomes

Several factors influenced muscle-related responses:

- Age and frailty — increased variability and vulnerability [11,12,29]
- Nutritional status — adequate protein intake associated with lean mass preservation
- Physical activity — resistance training mitigates muscle loss
- Co-interventions — amino acid supplementation and exercise preserved muscle outcomes [27]

These findings align with training research demonstrating that combined metabolic and mechanical stimuli determine body composition and strength adaptations [31].

3.6. Consistency and strength of evidence

Overall, evidence consistently indicates that SGLT2 inhibitors preferentially reduce fat mass while largely preserving skeletal muscle mass [1–4,7,8]. Functional outcomes appear neutral in most populations. Integration of exercise science findings strengthens interpretation by demonstrating that improved body composition can coexist with preserved or improved strength performance despite modest weight loss [31].

4. Discussion

The present systematic review provides a comprehensive synthesis of contemporary evidence regarding the effects of sodium–glucose cotransporter-2 inhibitors (SGLT2i) on skeletal muscle mass, muscle strength, and functional outcomes. Across multiple randomized controlled trials, prospective cohorts, and meta-analyses, SGLT2 inhibitors consistently induced modest but sustained reductions in body weight, predominantly driven by loss of fat mass rather than lean mass [1–4,7,8]. This pattern of body recomposition is clinically favorable in most patients with cardiometabolic disease, given the established links between excess adiposity—particularly visceral fat—and insulin resistance, systemic inflammation, dyslipidemia, and cardiovascular risk. Importantly, the magnitude of lean mass reduction observed in most studies was small and often below thresholds considered clinically meaningful for sarcopenia diagnosis, supporting the overall safety of SGLT2i therapy with respect to skeletal muscle health in non-frail populations.

However, the findings also highlight substantial heterogeneity across populations, underscoring that the muscle-related effects of SGLT2 inhibitors are not uniform. In middle-aged adults with T2DM and relatively preserved functional status, skeletal muscle mass and strength appeared largely stable over follow-up periods of 24–52 weeks [15–17]. In contrast, elderly populations

and patients with CKD exhibited greater variability in lean mass and strength responses, with selected subgroups demonstrating potentially clinically relevant declines [11–14,29]. These observations are biologically plausible given the baseline catabolic milieu present in aging and CKD, characterized by anabolic resistance, chronic inflammation, oxidative stress, metabolic acidosis, and reduced physical activity. In such contexts, even modest additional negative energy balance induced by glycosuria may tip the balance toward net muscle protein breakdown if not counterbalanced by adequate nutritional intake and mechanical loading of skeletal muscle. The dissociation observed between changes in skeletal muscle mass and changes in muscle strength warrants particular attention. Several studies reported stable handgrip strength despite small reductions in lean mass [13,14], consistent with the broader literature indicating that muscle function is not solely determined by muscle quantity but also by muscle quality, neuromuscular activation, fiber-type composition, mitochondrial function, and intramuscular fat infiltration. It is therefore plausible that reductions in adiposity and improvements in metabolic health associated with SGLT2i therapy may offset small reductions in muscle mass by enhancing muscle quality and insulin-mediated anabolic signaling. Conversely, in frail individuals with low baseline muscle quality, small structural losses may translate into disproportionate functional consequences. This highlights the importance of incorporating functional endpoints into future trials rather than relying exclusively on body composition metrics.

Methodological considerations also influence interpretation of the available evidence. Body composition assessment techniques differ in their sensitivity and susceptibility to confounding by hydration status. Bioelectrical impedance analysis (BIA), widely used in real-world studies, is particularly sensitive to shifts in total body water and extracellular fluid compartments. The osmotic diuretic effect of SGLT2 inhibitors may therefore artifactually exaggerate early reductions in lean mass measured by BIA, especially during the initial weeks of therapy. Dual-energy X-ray absorptiometry (DXA) provides more robust estimates of appendicular lean mass and skeletal muscle mass and suggests that true contractile tissue loss is modest [18]. These methodological nuances underscore the need for cautious interpretation of short-term lean mass changes and support the use of DXA or other high-fidelity imaging modalities in future research.

The temporal pattern of body composition change further contextualizes the clinical relevance of observed lean mass reductions. Early weight loss following SGLT2i initiation likely reflects a combination of fluid loss, glycogen depletion, and reductions in adipose tissue. Over longer

durations, metabolic adaptations favor increased fat oxidation and improved insulin sensitivity, potentially stabilizing muscle mass in the absence of severe caloric restriction. Long-term trajectories of skeletal muscle mass and function beyond one year remain insufficiently characterized, particularly in older adults and patients with CKD or HF. Given that SGLT2 inhibitors are intended for chronic use, long-term studies with repeated body composition and functional assessments are needed to determine whether small early changes in lean mass translate into meaningful functional outcomes over time.

From a clinical standpoint, the overall benefit–risk balance strongly favors the use of SGLT2 inhibitors in appropriate patients, given their robust cardioprotective and nephroprotective effects. The potential for small lean mass reductions should not deter clinicians from prescribing SGLT2 inhibitors in populations with clear indications. Nevertheless, the findings of this review support a more individualized approach to muscle health monitoring in selected high-risk groups. Older adults, patients with CKD, individuals with baseline frailty or low muscle mass, and those with limited physical activity may benefit from baseline and follow-up assessment of muscle-related outcomes, including handgrip strength and, where feasible, body composition.

Importantly, the evidence reviewed suggests that potential adverse effects on skeletal muscle are modifiable. Interventional studies combining SGLT2 inhibitors with resistance exercise and amino acid supplementation demonstrated preservation of muscle mass and function [27]. These findings align with established principles of sarcopenia prevention and management, emphasizing the central role of mechanical loading and adequate protein intake in maintaining muscle protein synthesis. In clinical practice, integrating lifestyle counseling—particularly resistance training and nutritional optimization—into the initiation and follow-up of SGLT2i therapy may represent a pragmatic and cost-effective strategy to mitigate potential muscle-related risks. Such integrated care models are especially relevant in geriatric, nephrology, and heart failure clinics, where multidisciplinary approaches to preserving functional capacity are increasingly recognized as essential components of high-quality care.

The present review also highlights important gaps in the existing literature. Functional outcomes such as gait speed, Short Physical Performance Battery scores, falls, and health-related quality of life are underreported in SGLT2i trials. Most available evidence derives from studies in T2DM populations, with limited direct data in HF and advanced CKD cohorts, despite the widespread use of SGLT2 inhibitors in these settings. Furthermore, few studies stratify outcomes by baseline frailty or nutritional status, limiting the ability to identify subgroups most

likely to benefit from targeted interventions. Standardization of sarcopenia definitions and outcome measures across studies would greatly enhance comparability and facilitate future meta-analyses focused on muscle-related endpoints.

In summary, the available evidence indicates that SGLT2 inhibitors promote favorable body recomposition with predominant fat mass loss and generally small, clinically neutral effects on skeletal muscle mass and function in non-frail adults. The heterogeneity observed across populations underscores the importance of individualized risk assessment and the integration of supportive lifestyle strategies in vulnerable groups. Future research should prioritize long-term, adequately powered trials with standardized assessments of muscle mass, muscle strength, and physical performance to fully elucidate the implications of chronic SGLT2i therapy for skeletal muscle health and functional aging.

5. Conclusions

The present systematic review synthesizes contemporary evidence on the effects of sodium–glucose cotransporter-2 inhibitors (SGLT2i) on skeletal muscle mass, muscle strength, and functional outcomes in adults treated for type 2 diabetes mellitus, chronic kidney disease, and heart failure. Across randomized controlled trials, prospective observational studies, and meta-analyses, SGLT2 inhibitors consistently produced modest but sustained reductions in body weight that were driven predominantly by loss of fat mass rather than lean mass [1–4,7,8]. In most non-frail adults, the magnitude of lean mass reduction observed was small and unlikely to be clinically meaningful in isolation, particularly when considered in the context of the substantial cardioprotective and nephroprotective benefits conferred by this drug class.

Importantly, the available evidence suggests that skeletal muscle mass and muscle strength are generally preserved during SGLT2i therapy in middle-aged adults with type 2 diabetes and relatively preserved functional status [15–17]. These findings support the overall muscle safety profile of SGLT2 inhibitors in typical outpatient populations and reinforce current guideline recommendations endorsing their widespread use in appropriate clinical settings. Nevertheless, heterogeneity across populations and study designs indicates that muscle-related effects are not uniform. Older adults, patients with chronic kidney disease, and individuals with baseline frailty or low muscle reserves may exhibit greater vulnerability to lean mass loss and functional decline [11–14,29]. In such populations, even small absolute reductions in skeletal muscle mass may have disproportionate clinical consequences, including increased risk of mobility limitation, falls, and loss of independence.

The dissociation observed between changes in muscle mass and changes in muscle strength and functional performance underscores the importance of considering both structural and functional endpoints when evaluating the musculoskeletal implications of pharmacological therapies. Preservation of muscle function may mitigate the clinical impact of small reductions in muscle mass in non-frail individuals, whereas in frail patients with compromised muscle quality, structural losses may translate into meaningful functional impairment. These considerations highlight the need for a more nuanced, patient-centered interpretation of body composition data in clinical practice.

From a practical standpoint, the findings of this review support the integration of muscle health considerations into the routine management of patients initiating SGLT2 inhibitor therapy, particularly in high-risk groups. Baseline and follow-up assessment of simple functional measures such as handgrip strength, alongside clinical evaluation of nutritional status and physical activity levels, may help identify individuals at risk of adverse muscle-related outcomes. The available evidence also suggests that potential muscle-related risks are modifiable. Co-interventions including resistance exercise programs and optimization of protein intake appear to attenuate lean mass loss and preserve muscle function during SGLT2i therapy [27]. Incorporating such lifestyle strategies into standard care pathways may enhance the overall benefit–risk profile of SGLT2 inhibitors, particularly in geriatric, nephrology, and heart failure populations.

The conclusions of this review should be interpreted in light of several limitations in the existing literature. Functional outcomes remain underreported in clinical trials of SGLT2 inhibitors, and long-term trajectories of skeletal muscle mass and function beyond one year are insufficiently characterized. Methodological heterogeneity in body composition assessment (DXA versus BIA) and variability in sarcopenia definitions further limit comparability across studies. Future research should prioritize long-term, adequately powered randomized trials with standardized assessment of muscle mass, muscle strength, physical performance, and patient-centered outcomes such as quality of life and disability. Such studies are particularly needed in older adults and patients with advanced chronic kidney disease or heart failure, who represent a growing proportion of the population receiving SGLT2 inhibitors.

In conclusion, SGLT2 inhibitors confer substantial cardiometabolic, cardiovascular, and renal benefits and promote favorable body recomposition characterized by predominant fat mass reduction. Their effects on skeletal muscle mass and function are generally small and clinically

neutral in non-frail adults but may be relevant in vulnerable populations. A personalized approach that combines pharmacological therapy with targeted lifestyle and nutritional strategies offers a pragmatic pathway to maximizing benefits while minimizing potential risks to skeletal muscle health.

Disclosure:

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Declaration of Generative AI and AI-Assisted Technologies

During the preparation of this work, the authors used ChatGPT-5.2 to improve grammar and language clarity. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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