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Review

Glucagon Like Peptide-1 Receptor Agonists for Sarcopenia and Muscle Wasting Disorders: A Systematic Review of Efficacy and Mechanisms

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ABSTRACT: Muscle wasting disorders, including sarcopenia and skeletal muscle atrophy, are increasingly prevalent among older adults and those with metabolic comorbidities. Sarcopenia, a progressive age-associated condition, involves the decline in skeletal muscle mass, strength, and physical performance, affecting millions of people globally. These disorders significantly elevate the risks of frailty, falls, and premature mortality, contributing to a growing burden on healthcare systems. Current interventions, including resistance exercise and dietary supplementation, have shown limited effectiveness, particularly among individuals with concurrent conditions such as type 2 diabetes (T2D). Notably, glucagon-like peptide-1 receptor agonists (GLP-1RAs), initially developed for glycemic and weight control, have demonstrated promising effects in preclinical models of muscle degeneration. In this review, we analyzed 20 preclinical and clinical studies on sarcopenia and muscle wasting disorders. Animal studies yielded promising results, including increased grip strength and enhanced skeletal muscle cross-sectional area (CSA), while body weight remained stable within a defined dosage range. Mechanistically, GLP-1RAs mitigate muscle wasting by upregulating myogenic factors (MyoD, MyoG), promoting mitochondrial biogenesis, and suppressing proteolysis (MuRF1, MAFbx) and inflammation via AMPK/SIRT1/NF-κB/Myostatin signaling. In contrast, limited clinical studies showed body weight reduction accompanied by a decline in lean mass following GLP-1RA treatment. Collectively, these results highlight the low dose-dependent anabolic potential of GLP-1RAs on skeletal muscle, while clinical evidence indicates simultaneous weight and lean mass loss. These findings suggest low-dose GLP-1RAs as potential therapy for sarcopenic obesity or early sarcopenia with metabolic comorbidities, warranting comprehensive clinical trials that incorporate multimodal strategies to preserve muscle mass during treatment.

Keywords: glucagon-like peptide-1, glucagon-like peptide-1 receptor agonist, skeletal muscle atrophy, sarcopenia, muscle aging, muscle wasting

INTRODUCTION

Progressive loss of skeletal muscle, whether due to aging or pathological conditions, contributes to increased morbidity and mortality [1] as seen in sarcopenia, muscle aging and skeletal muscle atrophy [2, 3]. These conditions share overlapping pathological mechanisms such as impaired protein synthesis, mitochondrial dysfunction,

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chronic inflammation, and hormonal dysregulation [4-6]. Sarcopenia, defined as an age-related decline in muscle mass and strength, has been widely studied [7-9], with reported prevalence ranging from 5% to 80% [10, 11], depending on diagnostic criteria and population characteristics [12]. Risk factors for sarcopenia include aging, sex, lifestyle [13], and comorbidities such as diabetes, obesity and chronic kidney disease (CKD) [14]. Clinically, sarcopenia increases the risk of frailty [15], falls [16], fracture [17], disability, mortality [18], and imposes economic burdens [19, 20].

Despite its clinical significance, therapeutic options for sarcopenia remain limited. First-line interventions such as physical exercise and protein supplementation offer modest benefits but face limitations in frail populations [21, 22]. Pharmaceutical approaches, including hormone therapies and myostatin inhibitors, have also shown limited efficacy [23, 24]. In this context, GLP-1 receptor agonists (GLP-1RAs), originally developed for T2DM and obesity [25], have emerged as promising therapeutic candidates [26, 27], due to systemic effects beyond glycemic control, including neuroprotection and cardioprotection [28, 29]. Preclinical studies suggest GLP-1RAs improve muscle and mitochondrial function [30, 31], reduce protein degradation [32], and improve insulin sensitivity [33] via SIRT1/AMPK pathways [34, 35]. However, concerns remain about possible lean mass loss during GLP-1RA–induced weight reduction [36, 37] as human studies show inconsistent outcomes, partly due to short treatment duration and heterogeneous regimens [38].

In this systematic review, we analyzed 20 preclinical and clinical studies investigating the effects of GLP-1RAs on muscle degenerative diseases, including sarcopenia, muscle atrophy, and muscle wasting, with a particular emphasis on sarcopenia. By synthesizing current evidence, we aim to address existing inconsistencies and provide insights for future research and potential therapeutic strategies.

METHODS

Search strategy

A systematic literature search was conducted on 10 August 2025 on PubMed, Web of Science and Embase databases to identify relevant articles and summarize their key findings. The keywords used were as follows: (Glucagon-like peptide-1 OR GLP-1 OR GLP1 OR Glucagon-like peptide-1 receptor agonists OR GLP-1RAs OR Semaglutide OR Liraglutide OR Dulaglutide) AND (Muscle atrophy OR Sarcopeni* OR Muscle aging OR Muscle wasting). Additionally, all the articles listed in the references were scrutinized for eligibility by our team members. The study adhered to the PRISMA guidelines.

Selection criteria

Inclusion criteria were as follows: (1) focusing on the efficacy and mechanisms of GLP-1 or GLP-1RA, (2) investigating sarcopenia, muscle atrophy or muscle wasting associated with aging, (3) available full-text articles that were published in English.
Exclusion criteria included: (1) non-English papers, (2) unavailability of full-text access, (3) irrelevant to GLP-1 or GLP-1RA and sarcopenia, muscle atrophy or muscle wasting associated with aging, (4) review articles, (5) publications limited to conference abstracts, letters or book chapters.

Study selection and data extraction

Study selection and data extraction were independently conducted by two researchers. Irrelevant and duplicated papers were identified and eliminated using Endnote based on their titles and abstracts. The remaining articles deemed potentially relevant were further assessed according to pre-defined inclusion and exclusion criteria. Any discrepancies were solved through consultation with a third researcher.

The following key information was extracted for analysis: first author, year of publication, study type, animal strain and species, gender, age, type of GLP-1RA used, method of drug administration, outcome measures, muscles examined, methods and techniques employed and other relevant data.

Data analysis

For preclinical studies, due to substantial heterogeneity in animal models and methodologies, we conducted a qualitative synthesis, along with stratified quantitative analyses for grip strength and CSA.

For clinical studies, a meta-analysis was performed when sufficient data were available. To evaluate the methodological quality and risk of bias of the included clinical studies, we applied the Mixed Methods Appraisal Tool (MMAT). Each criterion was assessed qualitatively, with responses categorized as *Yes* (criterion met), *No* (criterion not met), or *Can't tell* (information insufficient or unclear), providing an overview of methodological rigor without assigning numerical scores. A summary of key domains—including clarity of research questions, representativeness of the sample, ascertainment of exposure/outcome, control for confounders, completeness of outcome data, and adequacy of statistical analysis—is presented in Table 2. Additionally, study-type-specific

tools were used to complement the MMAT assessment: cohort and cross-sectional studies were evaluated using the Newcastle-Ottawa Scale (NOS), case series with the NIH Quality Assessment Tool, and randomized controlled trials (RCTs) with the Cochrane Risk of Bias 2 (RoB 2) Tool.

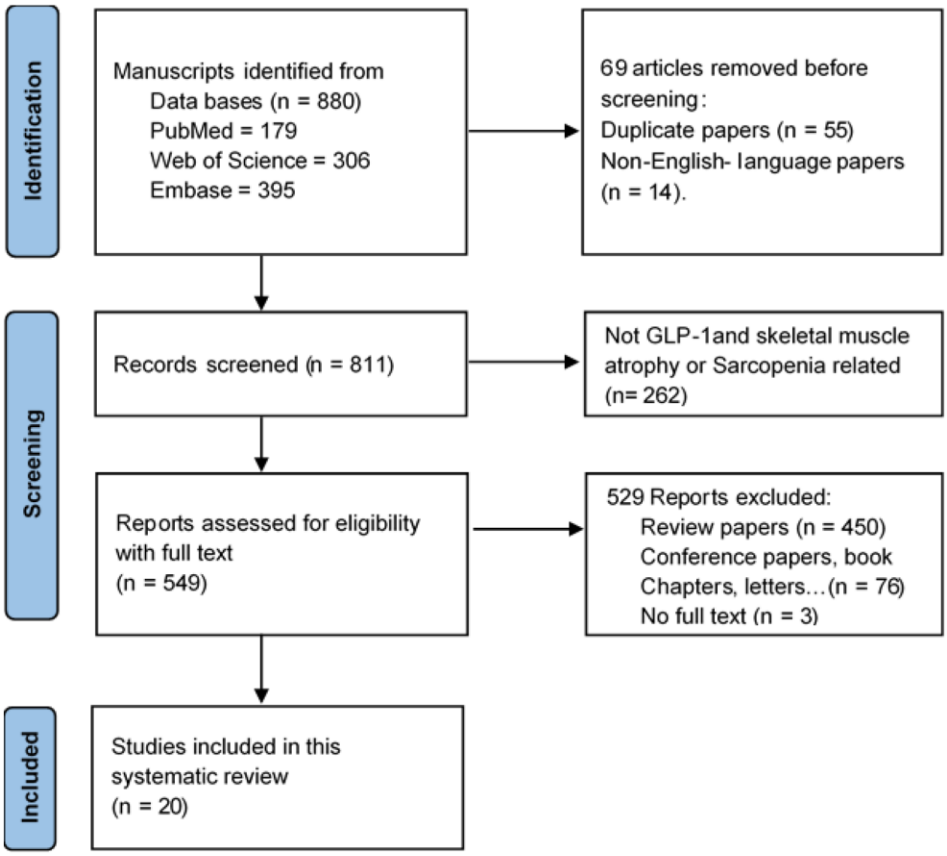

Figure 1. PRISMA 2020 flow diagram for the systematic review selection process.

RESULTS

Search results

The initial search yielded 880 original articles from three databases (395 from Embase, 306 from Web of Science and 179 from PubMed). After removing 55 duplicates and 14 non-English papers, 811 records remained for screening. Based on title and abstract screening, 262 papers were excluded as irrelevant. Subsequently, 450 review papers, 3 articles without full text, and 76 conference papers, book chapters or letters were excluded, resulting in 20 original articles that met the criteria. These 20 studies were included in this systematic review. The flowchart of the selection process is shown in Figure 1.

Quality and characteristics of the included studies

This systematic review included 20 studies published between 2016 and 2025, comprising 8 clinical studies and 12 basic studies (Table 1).

The quality of the 8 clinical studies was assessed using the MMAT, as well as other established tools including the NOS, NIH, and RoB 2. The results are summarized in Table 2 and Supplementary Tables 1–4. Overall, these studies were of high quality and considered appropriate for both qualitative and quantitative analyses. Detailed assessment outcomes are provided in the supplementary materials. The 8 clinical studies covered various designs (RCT [39], cohort [40], case series [41], cross-sectional [42-44], and observational analysis [45]) and populations (diabetes [39, 41, 45], sarcopenia/non-sarcopenia [42, 44], heart failure [43], expeditioners [40]). The 12 basic studies comprise 11 mice [32, 35, 39, 46-53], 2 rat [54, 55], and 1 C2C12 cell study [56]. Among the mice studies, 6 of them used C57BL/6N mice [32, 35, 46-48, 52], 3 used high-fat diets or diabetic mice [39, 49, 51], 2 used gene knockout mouse models [32, 57]. Most studies used male animals to avoid confounding effects of estrogen fluctuations on drug responses related to muscle and sarcopenia [32, 35, 40-45, 47]. Only 1 study used 24-month-old mice [41]; others used younger animals.

Stratified quantitative analyses of grip strength (**Table 3**) and CSA (**Table 4**) revealed considerable methodological diversity across studies. Among the included studies, 4 assessed hindlimb grip strength [50-52, 55], 2 evaluated forelimb grip strength [50, 51], and 2 measured grip strength across all four limbs [32, 35]. Regarding CSA measurements, 4 studies analyzed the tibialis anterior muscle [32, 35, 48, 55], 3 focused on the gastrocnemius [47, 52, 55], and 1 study simultaneously examined both the quadriceps and hamstrings, using female mice [46]. Only 1 study investigated the CSA of the soleus muscle [50]. The reported grip strength values ranged from 1.07 to 8.30 g/g, while CSA values varied widely from 714 to 59,000 μm². These discrepancies likely stem from differences in experimental conditions, including animal species and strain, age, sex, drug administration methods, and the specific muscle sections analyzed.

Table 1. Characteristics of included studies.

Study	Research type	Strain, species	Sex and age	Type of GLP-1 used and treatment methods	Overall functional markers of sarcopenia and GLP-1	Muscles collected	Methodology
Hong, Y. (2019) [32]	Basic research (Animal and cell experiments)	C57BL/6, DBA/2J-mdx mice, Glp1rflox/floxCre+ C2C12.	Male, 7 and 10 weeks old	Exendin-4(Ex-4) : i.p., and Dulaglutide: s.c. Dexamethasone(Dex) induced muscle atrophy: Ex-4 100 ng/day for 12 days; CKD-induced muscle atrophy: Ex-4 100 ng/day for 8 weeks; Duchenne muscular dystrophy model(mdx): Dulaglutide s.c., 1 mg/kg/week for 3 weeks; Dex: i.p., 20 mg/kg/day for 8 days.	Body weight, grip strength, food intake	Gastrocnemius (GA), tibialis anterior (TA), quadriceps (QD), extensor digitorum longus (EDL), and soleus (SOL).	CSA, limb hanging test, Immunohistochemistry. C2C12 transfection with siRNA GLP-1R, Western blot, qRT-PCR, ELISA, immunohistochemistry, serum analysis.
Ren, Q. (2022) [47]	Basic research (Animal experiment)	C57BL/6 mice	Male, 18 weeks old	Semaglutide: i.p., 30 nmol/kg/day for 12 weeks.	Body weight	GA	CSA, number and density of muscle fibers, myofiber type ratio, TEM, ELISA
Khin, P. P. (2021) [48]	Basic research (Animal experiment)	C57BL/6J mice	Male, 4 and 24 months old	Dulaglutide: s.c., 600 μg/kg/week for 4 weeks	Body weight, Grip strength, muscle mass, food intake	GA, TA, QD, EDL, and SOL	CSA, myofiber type ratio, Immuno-histochemistry, IF staining, Western blot, qRT-PCR.
Deng, F. (2023) [49]	Basic research (Animal and cell experiments)	Diabetic and non-diabetic mice, C2C12.	Male, 10 weeks old	Dulaglutide: i.p., 0.6 mg/kg per week for 10 weeks	Muscle mass	SOL	CSA, Western blot, Immunohistochemistry, Cell viability assays, qRT-PCR.
Chan, D. C. (2024) [50]	Basic research (Animal experiment)	ICR mice	Male, 10 weeks old	Exendin-4: s.c., 2.5 μg/kg/day for 4 weeks; Metformin: s.c., 300 mg/kg/day for 4 weeks;	Body weight, grip strength, muscle mass	TA, EDL, GA, SOL.	Blood glucose levels, histological analysis, CSA
Xiang, J. (2023) [35]	Basic research (Animal and cell experiments)	C57BL/6J mice. C2C12.	Male, 27 weeks old	Liraglutide: s.c., 400 μg/kg/d for 4 weeks; Semaglutide: s.c., 60 μg/kg/d for 4 weeks	Body weight, grip strength, muscle mass, FFM, food intake	GA, TA, QD, and SOL	Limb hanging test, CSA, SIRT1 inhibitor EX-527, Western blot, ELISA, IF, qRT-PCR, flow cytometry
Iwai, S. (2023) [51]	Basic research (Animal and	Diabetic KK-Ay mice, C2C12.	Male, 10 weeks old	Semaglutide: s.c., 3 nmol/kg every 3 days, for 6 weeks.	Body length, body weight, grip strength, Muscle mass,	GA	CSA, Micro CT imaging, Western blot, Immunohistochemist

	cell experiments)				psoas muscle mass index (cross sectional area/height2)		ry, IF, ELISA, qRT-PCR,
Xu, Q. (2025) [54]	Basic research (Animal and cell experiments)	Sprague-Dawley (SD) rats, C2C12	Not mentioned, 14 weeks old	Liraglutide: i.p., 0.4 mg/kg per day for 8 weeks	Body weight, muscle length and weight.	GA	CSA, Western blot, Immunohistochemistry, IF, high glucose impact on myotube morphology, β-galactosidase staining
Gurjar, A. A.r (2020) [55]	Basic research (Animal and cell experiments)	Sprague Dawley rats, C2C12.	Male and female 2 and 10 months old	Liraglutide : s.c., Freeze-Injury: 200 µg/kg, b.i.d, for 12 h-4 days Denervation: 200 µg/kg, b.i.d, for 3-7 days Dexamethasone-Induced Muscle Atrophy: 200 µg/kg, b.i.d, for 14 days. OVX model: 300 µg/kg, q.d, for 12 weeks.	Body weight, grip strength, muscle mass, food intake.	GA, TA	Footprint analysis, Wire hanging test, Echo-MRI, CSA, Western blot, Immunohistochemistry, immunoblotting, Rotarod, qRT-PCR, siRNA transfection, cAMP measurement, Pharmacological Inhibitors (SQ22356, H-89, ESI-09, SB203580, and PD98059).
Nguyen, T. T. N. (2020) [52]	Basic research (Animal experiment)	C57BL/6N mice, C2C12.	Male, 10 weeks old	Dulaglutide: s.c., 600 µg/kg on day 4 after immobilization for 7 days	Body weight, grip strength, muscle mass, food intake.	GA, TA, QD, EDL, and SOL	CSA of GA, Western blot, Histological analysis, qPCR
Kamiya, M. (2022) [46]	Basic research (Human, animal and cell experiments)	C57BL/6 mice. Human muscle specimens. C2C12.	Female, 8 weeks old	PF1801: s.c., Prophylactic treatment of C protein-induced myositis(CIM): 5.0 mg/kg/day for 14 days(0-14); Therapeutic treatment of CIM: 5 or 2.5 mg/kg/day for 14 days(7-21); Muscle tube necrosis induced by Fas Ligand:100 nM into medium, once. PF1801: s.c., 5.0 mg/kg/day + prednisolone 20 mg/kg ,14 days.	Body weight, grip strength, muscle weight	Human specimens: tibialis anterior muscle biopsy. Mice: QA and biceps femoris (hamstrings).	CSA, Immunohistochemistry, MG132 (a proteasome inhibitor), western blotting, IF staining, Time-lapse imaging of cells, Cell Viability Assays.
Fan, D. (2024) [56]	Basic research (Cell experiment)	C2C12	Cell Experiment	Liraglutide: 100, 200, 500 nmol/L, 48 h	Not investigated.	Not collected.	Western blot, ELISA, High-throughput transcriptome sequencing, MTT assay, qPCR, Differentially expressed mRNAs
Fan, DM. (2023) [39]	Basic and clinical research (RCT)	KK-Ay mice, T2DM patients, C2C12.	Male, Mice: 11-12 weeks old, Human: 45-70 years old.	Mice: Liraglutide: s.c., 250 µg/kg/d for 8 weeks Human: Not used	Body weight, total body muscle mass, skeletal muscle mass, fat mass, SMI, BMI, food intake, GLP-1 and DPP4 levels, blood glucose.	Lower limb muscle tissues were collected (specific names not mentioned).	DXA, ELISA, Real-time PCR, Western blot, IF, Generation of adenoviruses

Huang, Hsien-Hao (2024)[42]	Basic and clinical research (Cross-sectional study)	Sarcopenia/non-sarcopenia humans C2C12.	Male and female 82.5 ± 00.7 years old	Not used in human experiment. Cell: GLP-1(type not provided), 1 ng/mL, 10 ng/mL, 100 ng/mL	Body weight, height, BMI, ASMI, FM, FFM, gastrointestinal hormones (ghrelin, PYY and GLP-1), glucose.	Not collected.	Western blot, IF, ELISA, glucose uptake assays, seahorse metabolic analysis, flow cytometry, kinesin-1 activity, qPCR
Perna, S. (2016)[41]	Clinical research (Case series study)	overweight /obese T2DM patients	Male and female 68-75(68.2 2 ± 3.86) years old	Liraglutide: s.c., 3.0 mg per day, for 12-24 weeks. Metformin: per os, 2 g/day, for 24 weeks.	Body weight, height, BMI, SMI, total body fat mass, total body/legs/arms fat-free mass and android/ gynoid fat ratio (A/G), whole body scan.	Not collected	Physical activity assessment (PASE), DXA.
Osaka, T. (2023)[45]	Clinical research (Retrospective, longitudinal analysis).	T2DM patients	Male and female >70 years old	Lixisenatide; Glargine =1:1, for 1 week, (rote and dosage not provided).	Body weight, Body fat mass, FFM, ASM, SMI, BMI, fasting blood glucose, food intake	Not collected	Bioelectrical impedance analyzer(BIA).
Ren Q, (2025)[58]	Clinical research (Retrospective, cohort study)	T2DM patients	Male and female 65 - 79 years old	Semaglutide (rote and dosage not provided).	BMI, ASMI, Hand grip strength, Gait speed	Not collected	BIA
Tacke, M. (2013)[43]	Clinical research (Cross-sectional study)	Heart failure patients	Male and female 67.4 ± 10.2 years old	Not used external GLP-1.	Body weight, FFM and fat mass, SMI, ASM	Not collected	Resting energy expenditure, GLP-1, DXA, indirect calorimetry, ELISA, weighing scale, blood sampling.
Huang, H. H. (2022)[44]	Clinical research (Cross-sectional study)	Sarcopenia/non-sarcopenia humans	Male and female 86.9 years old	Not used external GLP-1.	Body weight, FFM and fat mass, BMI, Muscle strength, SMI, Nutritional status, Gastrointestinal hormone levels (Cholecystokinin , GLP-1, Peptide YY, Ghrelin, Nesfatin).	Not collected	BIA, handgrip strength test, Mini-Nutritional Assessment-Short Form, Blood sample, ELISA
Wandrag, L. (2017)[40]	Clinical research (Prospective cohort study)	Human: expeditioners	Male and female 19-59(34.9±9.2) years old	Not used external GLP-1.	Body weight, muscle mass (FFM, FM), metabolic and vascular markers (GLP-1, insulin, glucagon, triiodothyronine, adrenaline, noradrenaline, lactate, various adipokines)	Not collected	Anthropometry, BIA, blood sampling, ELISA, glucose oxidase, intra- and extracellular water, nitric oxide (NO), thyroid hormone panel, immunoassay kits.

Abbreviations of key elements mentioned in the table: DBA/2J-mdx mice: Duchenne muscular dystrophy model mice, $Glp1r^{flox/flox}Cre^{+}$ mice: selective knockout of the GLP-1 receptor (Glp1r) in muscle tissue, ICR mouse: Institute for Cancer Research mouse; Akt KO mice: Skeletal muscle - Akt knockout mice. Ex-4: Exendin-4, Dex: Dexamethasone; CKD: Chronic Kidney Disease; OVX: Ovariectomized animal; GA: Gastrocnemius, TA: tibialis anterior, QD: quadriceps, EDL: extensor digitorum longus, SOL: soleus; CSA: muscle fiber cross-sectional area; IF: Immunofluorescent staining. s.c.: subcutaneous injection. i.p.: intraperitoneal; FFM: fat free mass; FM: fat free mass; DXA: Dual energy x-ray absorptiometry; TEM: Transmission Electron Microscopy; AST: aspartate aminotransferase, ALT: alanine aminotransferase, TC: total cholesterol, TG: total triglycerides, LDL-c: low-density lipoprotein cholesterol, and HDL-c: high-density lipoprotein cholesterol, HbA1c: Glycosylated hemoglobin, PYY: Peptide YY. RCT: Randomized controlled trial, ASM: appendicular skeletal muscle mass. SMI: skeletal muscle mass index(kg/height2), BMI: body mass index. BIA: Bioelectrical impedance analyzer.

Table 2. MMAT critical appraisal table for clinical studies.

Study	Design	MMAT Category	Screening: Clear Research Question	Screening: Data Addressed Question	Representativeness of Sample	Ascertainment of Exposure/ Outcome	Control for Confounders	Completeness of Outcome Data	Statistical Analysis	Overall Quality	Key Biases/Limitations
Osaka, T. (2023) [45]	Cohort	Quantitative non-randomized	Yes	Yes	Yes	Yes (BIA for ASM)	Can't tell	Yes	Yes	Moderate	Small sample size, short follow-up
Ren Q, (2025) [58]	Cohort	Quantitative non-randomized	Yes	Yes	Yes	Yes (DXA for ASMI)	Yes	Yes	Yes	High	Large sample, but observational design
Wandrag, L. (2017) [40]	Cohort	Quantitative non-randomized	Yes	Yes	Yes	Yes (ultrasound)	Can't tell	Yes	Yes	Moderate	Limited adjustment for confounders
Huang, Hsien-Hao (2024) [42]	Cross-sectional	Quantitative descriptive	Yes	Yes	Yes	Yes (DXA)	No	Yes	Yes	Moderate	Cross-sectional limits causal inference
Tacke, M. (2013) [43]	Cross-sectional	Quantitative descriptive	Yes	Yes	Can't tell	Yes (CT imaging)	No	Yes	Yes	Moderate	Small sample, limited generalizability
Huang, H. H. (2022) [44]	Cross-sectional	Quantitative descriptive	Yes	Yes	Yes	Yes (BIA)	No	Yes	Yes	Moderate	No confounder control, cross-sectional
Perna, S. (2016) [41]	Case Series	Quantitative descriptive	Yes	Yes	Can't tell	Yes (DXA for SMI)	No	Can't tell	Yes	Low	No control group, small sample
Fan, D. M. (2023) [39]	RCT	Quantitative RCT	Yes	Yes	Yes	Yes (DXA, molecular markers)	Yes	Yes	Yes	High	Small sample size

Methodology: Each criterion is assessed qualitatively. Responses are reported as Yes (criterion met), No (criterion not met), or Can't tell (information insufficient or unclear). This approach provides an overview of methodological quality without assigning numerical scores.

As shown in Table 1 and 5, the GLP-1RAs used across these studies include Semaglutide [47, 51], Liraglutide [35, 39, 41, 54-56], Dulaglutide [48, 49, 52], Exendin-4 [32, 50], Froniglutide (PF1801) [46], and Lixisenatide [45]. The administration routes for GLP-1RAs were primarily subcutaneous (s.c.) [35, 46, 48, 50-52, 55], or intraperitoneal (i.p.) [32, 47, 49, 54] in animals, with direct application in cell cultures [42, 56]. Assessments aligned with sarcopenia diagnostics, measuring body weight [32, 35, 39-48, 50-52, 54, 55], grip strength [32, 35, 46, 48, 50-52, 55], and food intake [32, 35, 48, 52, 55], given the appetite-suppressing effects of GLP-1RAs. Additionally, 13 studies extracted muscle tissue from humans or mice [32, 35, 39, 46-52, 54, 55, 57], while 8 clinical studies measured body functions and blood samples from individuals [39-45]. Eight studies investigated the signaling pathways or underlying mechanisms of GLP-1RAs effect [32, 35, 46-49, 51] (Table 6).

The impact of GLP-1RAs in preclinical studies

Drug administration methods and their impact on body weight and muscle weight in preclinical studies.

Dosage and duration are essential for GLP-1RA treatment. Although most studies administered GLP-1RAs at approximately 100 μg/kg/day [47-49], the dosage varied widely across studies, from as low as 0.1 μg/day of Exendin-4 for 8 weeks [32] to as high as 400 μg/kg/day of Liraglutide for 8 weeks [54]. Hence, to analyze the effects of GLP-1RA dosage on body weight, we categorized GLP-1RA regimens into three dosage groups, low dosage group (0.1μg/day - 4.11 μg/kg/d or 0.1μg/day - 12.34μg/kg, every 3 days) [32, 50, 51], medium dosage group (60 μg/kg/d - 142.86 μg/kg/d) [32, 35, 47-49, 52] and high dosage group (250 μg/kg/d - 5000 μg/kg/d) [35, 39, 46, 54, 55]. Notably, the study conducted by Xiang et al. [35] included both the medium dosage group (Semaglutide: 60 μg/kg/d for 4 weeks) and the high dosage group (Liraglutide: 400 μg/kg/d), as it involved two distinct drug administration regimes. Therefore, for quantification, we adopted drug administration models reported in the articles rather than relying on the number of studies.

Low dose of GLP-1RA were generally associated with weight gain, medium doses showed no significant effect, and high doses resulted in weight reduction

Table 3. Stratified quantitative synthesis table for grip strength.

Tested limb	Species and strain	Sex	Age	Type of GLP-1	Models	Drug administration methods	Groups	Grip Strength (g/g)	SD	n	P value
Hindlimb	ICR mice[50]	Male	10 weeks old	Exendin-4	Muscle wasting in diabetic mice	2.5 μg/kg/day for 4 weeks;	Control	3.45	0.21	8	
							STZ	2.86	0.20	8	
							STZ+Ex-4	3.37	0.31	8	
	Diabetic KK-A^{y} mice[51]			Semaglutide	CLD-induced muscle atrophy in diabetic mice	3 nmol/kg every 3 days, for 6 weeks.	Vehicle + ND	5.25	1.30	10	Veh + ND: Veh + DDC = ** <0.01
							Semaglutide + ND	5.40	1.35	10	
							Vehicle + DDC	2.00	0.40	10	
							Semaglutide +DDC	3.55	0.60	10	Veh + DDC: Sem + DDC = * <0.05
	C57BL/6 N mice [52]			Dulaglutide	Disuse muscle atrophy mice	600 μg/kg on day 4 after immobilization for 7 days	CV	1.70	0.16	6-7	CV:CD= * < 0.05
							CD	2.00	0.05		CV:IV= *** < 0.001
							IV	1.07	0.07		IV:ID = * < 0.05
							ID	1.25	0.12		
	Sprague Dawley rats [55]	Male	8 weeks old	Liraglutide	liraglutide in freeze injury	200 μg/kg, b.i.d, for 12 h-4 days	Control 48h	6.80	0.40	5	control: Injury 48h = ** < 0.01
							Freeze injury 48h	3.80	0.18		
							Injury + lira 48h	5.60	0.70		
							Control 96h	8.30	0.40		
							Freeze injury 96h	4.20	0.20		control 96h: Injury 96h = *** < 0.001
							Injury + lira 96h	8.00	0.30		Injury 96h: Injury + Lira 96h = # < 0.001
		Female	8 weeks old		Liraglutide in dexamethasone- induced atrophy.		Control	3.82	0.20	6	Control: dexamethason = ** < 0.01
							Dex	2.70	0.20		dexamethason: dexamethason + Lira = ## < 0.01
							Dex + lira	3.57	0.18		
Forelimb	ICR mice [50]	Male	10 weeks old	Exendin-4	Muscle wasting in diabetic mice	2.5 μg/kg/day for 4 weeks;	Control	3.31	0.05	8	Control:STZ= * < 0.05
							STZ	2.55	0.20	8	
							STZ+Ex-4	3.50	0.10	8	STZ:EX-4=# <0.05
	Diabetic KK-A^{y} mice [51]	Male	10 weeks old	Semaglutide	CLD-induced muscle atrophy in diabetic mice	3 nmol/kg every 3 days, for 6 weeks.	Vehicle + ND	4.50	0.35	10	Veh + ND: Veh + DDC = ** <0.01
							Semaglutide + ND	4.40	0.30	10	
							Vehicle + DDC	1.60	0.30	10	
							Semaglutide +DDC	2.60	0.30	10	Veh + DDC: Sem + DDC = * <0.05
Limbs (four)	C57BL/6 mice [32]	Male	10 weeks old	Exendin-4(Ex-4)	Dex-induced muscle atrophy in mice	Ex-4 100 ng/day for 12 days	Con + Vehicle	7.10	0.30	5	Con + Vehicle : Con +Dex= ** <0.01
							Con +Dex	5.30	0.20	5	Con + Dex: Ex-4 + Dex= ** <0.01
							Ex-4 + Vehicle	6.90	0.35	5	

						Ex-4 + Dex	6.40	0.25	5	
				CKD-induced muscle atrophy in mice	Ex-4 100 ng/day for 8 weeks;	Vehicle + Sham	3.95	0.08	5-7	Sham + Vehicle: CKD + Vehicle = ** < 0.01
						Ex-4 + Sham	4.10	0.10	5-7	CKD Vehicle: Ex-4= ** < 0.01
						Vehicle + CKD	3.20	0.25	5-7	
						Ex-4 + CKD	4.10	0.20	5-7	
DBA/2J-mdx mice [32]	Male	7 weeks old	Dulaglutide	Duchenne muscular dystrophy in DBA/2J-mdx mice.	1 mg/kg/week for 3 weeks;	Vehicle	3.50	0.10	9-10	Vehicle: Dulaglutide= ** < 0.01
						Dulaglutide	4.27	0.15	9-10	
C57BL/6J mice [35]	Male	27 weeks old	Liraglutide or Semaglutide	Semaglutide or Liraglutide in obesity-induced muscle atrophy	LIRA 400 μg/kg/d for 4 weeks SEMA 60 μg/kg/d for 4 weeks	Control	6.40	0.45	6	control: HFD= * < 0.05
						LIRA	6.25	0.60		
						SEMA	6.15	0.65		Control: HFD+LIRA = * < 0.05
						HFD	3.60	0.45		Control: HFD+SEMA = * < 0.05
						HFD+LIRA	5.42	0.60		HFD: HFD+LIRA = # < 0.05
						HFD+SEMA	5.10	0.55		HFD: HFD+SEMA = # < 0.05

As illustrated in Table 5 and Fig. 2A, two out of three studies in low dose group models (0.1 - 4.11 μg/kg/d), including Dex, CKD and CLD-induced muscle atrophy in mice, exhibited an increase in body weight [32, 51]. In contrast, another study reported a reduction in body weight in diabetic mice with muscle wasting, compared to the vehicle group [50] ($P < 0.05$).

In the medium dosage group (60 - 142.86 μg/kg/d) (Fig. 2A), half of the studies involving murine models of muscle wasting, including sarcopenic obesity [47], muscle atrophy [35], and diabetic sarcopenia in young mice [48], exhibited a reduction in body weight relative to their vehicle-treated controls ($P < 0.05$). In contrast, other mouse models, namely Duchenne muscular dystrophy [32], disuse-induced muscle atrophy [52], and aged sarcopenia mice [48], did not display apparent changes in body weight following treatment.

In the high dosage group (250 - 5000 μg/kg/d) (Fig. 2A), 4 of 5 studies, including diabetic and obesity-induced muscle atrophy models in mice [35, 39], PF1801 (2.5 or 5.0 mg) + PSL (20 mg) treatment of CIM [46], and DEX-induced muscle atrophy in rats [55], showed reduced body weight ($P < 0.05$). In contrast, PF1801 monotherapy (5.0 mg) in the same study [46] showed no significant difference from the vehicle group.

Different GLP-1RAs exert varying effects on body weight in animals.

As the researchers used different kinds of GLP-1RAs, we also analyzed the effects of different GLP-1RAs on body weight (Fig. 2B). Exendin-4 increased body weight in DEX and CKD induced muscle atrophy models in mice [32], but decreased it in diabetic muscle wasting model [50]. Semaglutide in the CLD-induced muscle atrophy model showed increased body weight [51], while the sarcopenic obesity and obesity-induced muscle atrophy models demonstrated a reduction [35, 47] ($P < 0.05$). Dulaglutide reduced body weight in aged sarcopenic and young mice [48], whereas no significant changes were observed in the disuse-induced atrophy model [52] and the Duchenne muscular dystrophy model [32]. As for liraglutide, it reduced body weight in two out of three studies involving diabetic and obesity-induced muscle atrophy models in mice, whereas no significant change was observed in the DEX-induced muscle atrophy model in rats [35, 39, 55]. This pronounced reduction in body weight may be attributable to the relatively high dosage applied (250–5000 μg/kg/day). One study evaluated five models of CIM using Froniglutide [46]. In the prophylactic treatment setting, mice received PF1801 at 5.0 mg alone or in combination with prednisolone (PSL) 20 mg; in the therapeutic setting, treatment regimens included PF1801 5.0 mg alone, PF1801 5.0 mg + PSL 20 mg, and PF1801 2.5 mg + PSL 20 mg/kg. Froniglutide monotherapy did not significantly affect body weight, whereas combination therapy with prednisolone was associated with a reduction in body weight ($P < 0.01$).

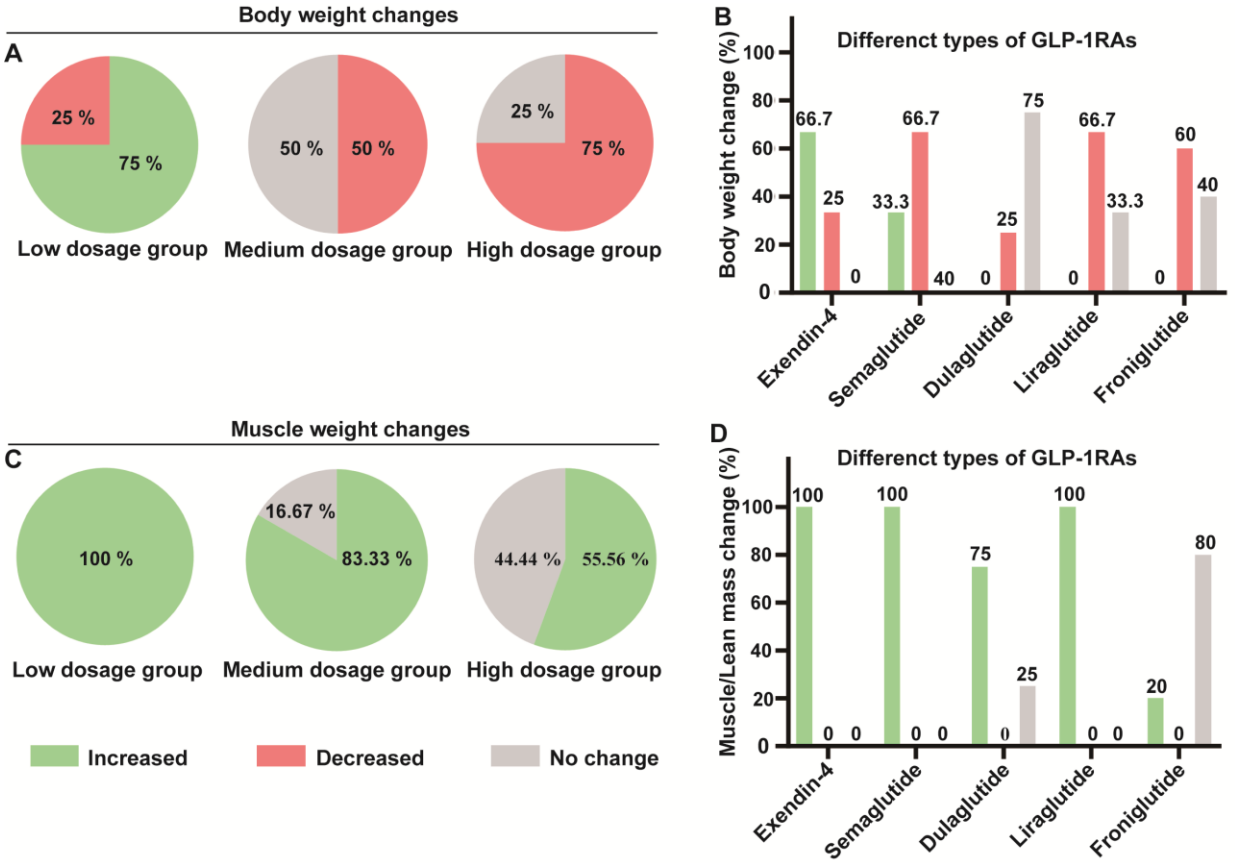

Figure 2. Effects of different GLP-1RA dosages and types on body weight and muscle weight. Panels **A** and **C** show the effects of varying GLP-1RA dosages on body weight (**A**) and muscle weight (**C**), categorized into low (0.1 μg/day – 4.11 μg/kg/day), medium (60 μg/kg/day – 142.86 μg/kg/day), and high (250 μg/kg/day – 5000 μg/kg/day) dosage groups. Panels **B** and **D** illustrate the effects of different GLP-1RA types on body weight (**B**) and muscle weight (**D**). Percentages represent the proportion of studies using each type within the respective classification group. Color coding: green indicates an increase, red indicates a decrease, and grey indicates no significant change.

GLP-1RAs increased muscle mass at low and medium doses, but high doses yielded inconsistent effects across preclinical models.

All three studies investigating the effects of low-dose GLP-1RA administration (0.1–4.11 μg/kg/day) on muscle weight (Fig.2 C), including models of Dex- or CKD-induced muscle atrophy[32], CLD-induced atrophy [51], and muscle wasting in diabetic mice models [50], reported increased muscle mass ($P < 0.05$).

In the medium-dose range (60–142.86 μg/kg/d), five models across six studies, Duchenne muscular dystrophy [32], sarcopenic obesity [47], disuse-induced atrophy [52], aged sarcopenia [48], and obesity-induced atrophy [35], showed increased muscle mass ($P < 0.05$). The remaining one study with young mice [48], reported no change in lean mass ($P < 0.05$).

Among the 5 studies classified within the high-dosage group (250–5000 μg/kg/d), increased muscle weight was observed in multiple models, including diabetic muscle atrophy [39], obesity-induced muscle wasting in mice [35], Dex-induced muscle atrophy in rats [55], diabetic SD rats [54], and mice receiving prophylactic treatment for CIM with PF1801 (5.0 mg/kg/d) + PSL (20.0 mg/kg/d)[46]. In contrast, other models from the same study by Kamiy et al. [46], those receiving either prophylactic treatment with PF1801 alone (5.0 mg/kg/d) or therapeutic interventions using PF1801 alone (5.0 mg), PF1801 combined with PSL (PF1801 5.0 mg + PSL 20 mg; PF1801 2.5 mg + PSL 20 mg/kg), did not exhibit significant changes in muscle weight.

Exendin-4, Semaglutide, Liraglutide, and Dulaglutide increase muscle mass, whereas Froniglutide shows no significant effect.

To investigate whether different GLP-1RAs have varied effects on muscle massWe also analyzed the effects of different types of GLP-1RAs on muscle weight (Fig. 2D). All of the models (100%) using Exendin-4, Semaglutide

and Liraglutide reported an increase in muscle weight [32, 35, 39, 47, 50, 51, 54, 55]. Most experimental models treated with Dulaglutide demonstrated an increase in muscle mass, including the Duchenne muscular dystrophy model [32], the disuse-induced muscle atrophy model [52], and the aged sarcopenia mice as described in Khin's study [48]. Interestingly, the same study by Khin [48], reported no significant change in muscle mass following Dulaglutide treatment in young mice, suggesting that its beneficial effects may be limited to aged sarcopenic populations. Froniglutide was evaluated in five mouse models of CIM [46]. Increased muscle weight was observed only in the prophylactic treatment group receiving PF1801 (5.0 mg/kg/d) combined with PSL (20.0 mg/kg/d). In contrast, no significant change was noted in the remaining models, which included prophylactic treatment with PF1801 alone (5.0 mg/kg/d) and therapeutic regimens using PF1801 alone (5.0 mg) or combined with PSL (5.0 mg + 20.0 mg and 2.5 mg + 20.0 mg/kg). Additionally, the study of Deng et al. [49] did not report any data on muscle weight change.

Table 4. Stratified quantitative synthesis table for CSA.

Muscle type	Species and strain	Sex	Age	Type of GLP-1	Models	Drug administration methods	Group	CSA (μm²)	SD	n	P value
Tibialis Anterior	C57BL/6 mice [32]	Male	10 weeks old	Exendin-4(Ex-4)	Dex- induced muscle atrophy in mice	Ex-4 100 ng/day for 12 days	Con + Vehicle	8000	800	5	CSA Vehicle: Vehicle +ex-4= ** Dex: Dex +ex-4= **
							Con +Dex	5000	600	5	Grip- Dex: Dex +ex-4= **
							Ex-4 + Vehicle	9500	900	5	
							Ex-4 + Dex	7750	700	5	
					CKD-induced muscle atrophy in mice	Ex-4 100 ng/day for 8 weeks;	Ex-4 + Dex	6350	300	5-7	Sham + Vehicle: CKD + Vehicle = ** < 0.01
							Vehicle + Sham	6500	250	5-7	CKD Vehicle: Ex-4= ** < 0.01
							Ex-4 + Sham	4400	250	5-7	
							Vehicle + CKD	5750	200	5-7	
	DBA/2J-mdx mice [32]		7 weeks old	Dulaglutide	Duchenne muscular dystrophy in DBA/2J-mdx mice.	1 mg/kg/week for 3 weeks;	Vehicle	4000	300	9-10	Vehicle: Dulaglutide= ** < 0.01
							Dulaglutide	5250	300	9-10	
	C57BL/7N mice [48]		4 months old	Dulaglutide	Diabetic sarcopenia in young mice	600 μg/kg/week for 4 weeks	Vehicle Young	5600	120	5-8	Vehicle Young: Dulaglutide Young =< 0.01 **
							Dulaglutide Young	6600	200		Vehicle Young: Vehicle Aging = < 0.01 **
			24 months old		Diabetic sarcopenia in aged mice		Vehicle aging	2100	100		Vehicle aging; vehicle dulaglutide = < 0.01 **
							Dulaglutide aging	4250	160		
	C57BL/6J mice [35].		27 weeks old	Liraglutide or Semaglutide	Semaglutide or Liraglutide in obesity-induced muscle atrophy	LIRA 400 μg/kg/d for 4 weeks SEMA 60 μg/kg/d for 4 weeks	Control	2200	300	6	control: HFD= * < 0.05
							LIRA	2150	720		
							SEMA	2240	300		
							HFD	1400	140		
							HFD+LIRA	2240	160		HFD: HFD+ LIRA = # < 0.05
							HFD+SEMA	1860	240		HFD: HFD+ SEMA = # < 0.05

	Sprague Dawley rats [55]		8 weeks old	Liraglutide	liraglutide in freeze injury	200 μg/kg, b.i.d, for 12 h-4 days	Control	3100	200	5	Injury: Injury + Lira = # < 0.05
							Freeze injury	2260	370		
							Injury + lira	3500	250		
Gastrocnemius	C57BL/6J mice[47]	Male	18 weeks old	Semaglutide	Sarcopenic obesity in obese mice	30 nmol/kg/day for 12 weeks.	NC	59500	1000	6	NC: HFD < 0.05
							HFD	51000	2500	12	HFD: HFD +S < 0.05
							HFD+S	55000	2000	6	
	C57BL/6N mice [52]	Male	10 weeks old	Dulaglutide	Disuse muscle atrophy mice	600 μg/kg on day 4 after immobilization for 7 days	CV	17000	500	6-7	CV: CD = < 0.05
							CD	18000	200		CV: IV = < 0.01
							IV	8700	600		IV: ID = < 0.001
							ID	11900	600		
	Sprague Dawley rats [55]	Male	8 weeks old	Liraglutide	liraglutide in Denervation	200 μg/kg, b.i.d, for 12 h-4 days	Control	2680	150	5-8	Control: denervation = *** < 0.001
							Denervation	900	50		Control: denervation + LIRA = ** < 0.01
							Denervation + lira	1625	75		denervation: denervation + Lira = ### < 0.001
		Female	8 weeks old		Liraglutide in dexamethasone-induced atrophy.		Control	939	65	6-12	Control: dexamethason = * < 0.05
							Dex	714	30		dexamethason: dexamethason + Lira = # < 0.05
							Dex + lira	955	45		
		Female	40 weeks (10 months) old		liraglutide in ovariectomy-induced atrophy	300 μg/kg, q.d, for 12 weeks.	Control	2000	150	3-10	Control: OVX = *** < 0.001
							OVX	1350	110		
							OVX + lira	1760	90		OVX: OVX + LIRA = # < 0.05
Quadriceps	C57BL/6 mice [46]	Female	8 weeks old	PF1801 (Froniglutide)	Prophylactic treatment of CIM in mice: PF1801 5.0 mg;	5.0 mg/kg/day for 14 days (0-14);	Vehicle	1350	200	5	Vehicle: PF1801, CIM=* < 0.05
							PSL	1390	120	5	Vehicle: PSL + PF1801=** < 0.01
							PF1801	1900	100	5	PSL: PF1801, CIM= * <0.05
							PSL + PF1801	2000	400	5	PSL: PSL + PF1801= ** <0.01
							CIM (-)	1970	210	4	
					Therapeutic treatment of CIM in mice: PF1801 5.0 mg;	5 or 2.5 mg/kg/day for 14 days (7-21)	Vehicle	1390	100	5	Vehicle: CIM=** < 0.01
							PSL	1100	230	5	Vehicle: PSL + PF1801 5mg =* < 0.05
							PF1801 5mg	1550	100	5	PSL: PSL + PF1801 5mg, CIM= ** <0.01
							PSL + PF1801 2.5mg	1500	200	5	PSL :PF1801 5mg, PSL + PF1801 2.5mg= * <0.05
							PSL + PF1801 5mg	1800	90	5	PF1801 5mg: CIM = * < 0.05
							CIM (-)	1930	200	4	PSL + PF1801 2.5mg: CIM = * < 0.05
Hamstrings					Prophylactic treatment of CIM in mice: PF1801 5.0 mg;	5.0 mg/kg/day for 14 days (0-14);	Vehicle	1100	290	5	Vehicle; PF1801, PSL + PF1801, CIM=** < 0.01
							PSL	1260	300	5	
							PF1801	1250	100	5	PSL: PF1801, PSL + PF 1801= ** <0.01
							PSL+PF1801	1275	100	5	
							CIM (-)	1120	80	4	

					Therapeutic treatment of CIM in mice: PF1801 5.0 mg;	5 or 2.5 mg/kg/day for 14 days (7-21)	Vehicle	1090	225	5	
							PSL	880	280	5	Vehicle: PSL + PF1801 5mg, CIM=** < 0.01
							PF1801 5mg	1550	150	5	Vehicle: PF1801 5mg =* < 0.05
							PSL + PF1801 2.5mg	1495	50	5	PSL: PF1801 5mg, PSL + PF1801 2.5mg, PSL + PF1801 5mg, CIM = ** <0.01
							PSL + PF1801 5mg	1650	250	5	PSL + PF1801 2.5mg: CIM = * < 0.05
							CIM (-)	2000	200	4	
Soleus	ICR mice[50]	Male	10 weeks old	Exendin-4	Muscle wasting in diabetic mice	2.5 μg/kg/day for 4 weeks;	Control	1850	150	8	Control: STZ-4=* < 0.05
							STZ	1400	100	8	STZ: EX-4=* < 0.05
							STZ+Ex-4	1800	190	8	

Abbreviations mentioned in the table: STZ: streptozotocin; CLD: chronic liver disease; ND: normal diet; DDC: diethoxycarbonyl-1,4-dihydrocollidine (DDC diet); CV: control + vehicle; CD: control + dulaglutide; IV: immobilization + vehicle; ID: immobilization + dulaglutide; Con: control; SEMA: Semaglutide; HFD: high fat diet; LIRA: Liraglutide; PSL: prednisolone; CIM: C protein-induced myositis.

Different GLP-1 receptor agonists demonstrated distinct dose–response profiles.

Notably, the GLP-1RAs used in these studies exhibited distinct dosage profiles: Exendin-4 was primarily administered at low doses (0.1–2.5 μg/kg/day); Semaglutide at medium doses (12.34–123.4 μg/kg/day); Dulaglutide also at medium doses (100 μg/kg/day or 600–1000 μg/kg/week); Liraglutide at high doses (250–400 μg/kg/day); and Froniglutide at very high doses (2500–5000 μg/kg/day). Therefore, the varying effects of different GLP-1RAs across models may be attributed to differences in dosage and treatment duration. Overall, GLP-1RAs tended to have minimal impact on body weight at lower doses, while higher doses were associated with weight reduction. In general, these agents showed a consistent trend of improving muscle strength.

Effects of the GLP-1RAs on grip strength and muscle fiber cross-sectional area (CSA)

Most animal models across the 12 studies—including rats, mice, and genetically modified strains—reported improvements in grip strength and increases in the CSA of skeletal muscle fibers (Table 3 and Table 4). However, the studies by Ren et al. [47], Deng et al. [49], and Xu et al. [54], reported an increase in CSA only, without mention grip strength or other functional markers. In contrast, Fan et al. [39] reported neither grip strength nor CSA of muscle fibers.

Mechanism of action of the GLP-1Ras

Among the included studies, eight articles (shown in Table 6) investigated the mechanisms of action of GLP-1RAs. Their effects on skeletal muscle atrophy and sarcopenia were primarily linked to five biological domains: systemic and muscle-specific metabolism, mitochondrial dynamics, oxidative stress response, the ubiquitin–proteasome system, and inflammation/necroptosis. These mechanisms are summarized in Figure 3.

GLP-1RAs improve muscle and metabolic function via multiple signaling pathways

GLP-1RAs, initially developed for diabetes treatment, consistently demonstrated muscle-preserving and anti-atrophic effects, along with systemic metabolic benefits, across all eight referenced studies [32, 35, 46, 48, 51, 52, 54, 55]. For instance, Gurjar et al. [55] identified GLP-1R–cAMP signaling as a mediator of PKA/CREB, EPAC/PI3K/AKT, p38 MAPK, and ERK1/2 pathways. Xiang et al. [35] highlighted SIRT1 involvement, while Iwai et al. [51] described the regulatory roles of GCN2/eIF2α/ATF4, Sestrin2 expression, mTORC1, and p70S6K. Collectively, these pathways contribute to enhanced muscle mass and function through NF-κB/MSTN-mediated upregulation of MyoD and Myogenin. Additionally, Liraglutide activates the YAP/TAZ signaling pathway, leading to the downregulation of the aging marker P21 and upregulation of Cyclin D1, thereby alleviating high glucose-induced myocyte aging [54]. Furthermore, GLP-1RAs can regulate muscle and body metabolism by impacting insulin levels and glucose metabolism. The study by Xiang et al. reported that Liraglutide improved glucose tolerance, enhanced insulin sensitivity, and upregulated GLUT4 expression in diabetic mouse models through the SIRT1 signaling pathway and contributed to body

metabolism. The study of Hong et al. [32] found that GLP-1RAs significantly alleviated muscle wasting by modulating the PKA/AKT signaling pathway, inhibiting NF-κB activity, reducing GR nuclear translocation, and downregulating MSTN expression in the Dex-induced muscle atrophy model. Similar molecular mechanisms were also observed in CKD induced muscle atrophy and DBA/2J-mdx mice models, further supporting the anti-atrophic potential of GLP-1RAs.

Figure 3. **Schematic representation of five major mechanistic domains through which GLP-1RAs act on muscle atrophy**: metabolic function, mitochondrial dynamics, oxidative stress and antioxidant response, UPS, and inflammation/necroptosis. Upward black arrows indicate increased expression, activation, or functional improvement of the corresponding biological process or biomolecule, while downward black arrows indicate downregulation or inhibition. Specifically, GLP-1RAs improve mitochondrial function by upregulating PGC-1α, mtTFA, SIRT1 thereby promoting mitochondrial biogenesis, while downregulating ROS production and PGAM5 expression. They also enhance oxidative stress defense and antioxidant response by increasing antioxidant gene expression (Hmox1, Nqo1, Gstm3, Nfe2l2, Gclm) and reducing hepatic and muscular ROS (H_2O_2, 4-HNE, GCN2).

GLP-1RAs improve mitochondrial Dynamics and Function in Skeletal Muscle

As the primary structural and locomotive system of the body, skeletal muscles depend heavily on mitochondria, the key energy-producing organelles of the cells. Consequently, these studies examined the effects of GLP-1RAs on mitochondrial function and found that sarcopenia and muscle atrophy are closely associated with mitochondrial dynamics. GLP-1RAs have been reported to promote mitochondrial biogenesis, primarily through upregulation of PGC-1α and mtTFA via the activation of AMPK, SIRT1, and the GLP-1R/cAMP/PKA/AKT signaling cascade [32, 48, 51]. Meanwhile, Khin et al. [48] reported increased expression of OPA1, which

supports mitochondrial fusion and cristae remodeling, thereby enhancing mitochondrial dynamics.

Table 5. Drug administration methods and the effects on skeletal muscles.

Study	Type of GLP-1RA and Route	Dosage, and duration	Dosage group	Disease models	Effect on body weight	Effect on muscle mass	Effect on grip strength or muscle function	Effect on CSA
Hong, Y. (2019) [32]	Exendin-4(Ex-4) i.p. and Dulaglutide s.c.	Dex-induced muscle atrophy (Dex-model): Ex-4 0.1 μg/day for 12 days; CKD-induced muscle atrophy: Ex-4 0.1 μg/day for 8 weeks; Duchenne muscular dystrophy: Dulaglutide 1000 μg/kg/week for 3 weeks.	Low Low Medium	Dex-induced muscle atrophy in mice; CKD-induced muscle atrophy in mice; Duchenne muscular dystrophy in DBA/2J-mdx mice.	Ex-4 in Dex-model and CKD-induced muscle atrophy: ↑↑ Dulaglutide in Duchenne muscular dystrophy: ≈	Ex-4 in Dex-model and CKD-induced muscle atrophy model: ↑↑ Dulaglutide in Duchenne muscular dystrophy: ↑	Ex-4 in Dex-model : ↑↑ Ex-4 in CKD mice: ↑↑ Dulaglutide in Duchenne muscular dystrophy: Grip strength ↑↑, Four-limb suspension time ↑	Ex-4 in Dex-model and CKD-induced muscle atrophy model: ↑↑ Dulaglutide in Duchenne muscular dystrophy: ↑↑
Chan, D. C. (2024) [50]	Exendin-4 s.c.	2.5 μg/kg/day for 4 weeks;	Low	Muscle wasting in diabetic mice	Exendin-4: ↓	Exendin-4: ↑	Exendin-4 : forelimb grip strength↑ hindlimb grip strength ≈	Exendin-4: ↑
Iwai, S. (2023) [51]	Semaglutide s.c	Semaglutide: 12.34 μg/kg, every 3 days, for 6 weeks.	Low	CLD-induced muscle atrophy in diabetic mice	↑	↑(Gastrocnemius muscle weight)	↑(Both forelimb and hindlimb grip strength)	↑
Ren, Q. (2022)[47]	Semaglutide i.p	123.4 μg/kg/day for 12 weeks.	Medium	Sarcopenic obesity in obese mice	↓↓(29.67%)	↑↑	Not measured.	↑↑
Nguyen, T. T. N. (2020) [52]	Dulaglutide s.c.	600 μg/kg once, on day 4 after immobilization for 7 days	Medium	Disuse muscle atrophy mice	≈	↑	↑↑	↑
Deng, F. (2023)[49]	Dulaglutide i.p.	600 μg/kg/week for 10 weeks	Medium	Diabetic sarcopenia mice	Not mentioned	Not mentioned	Not measured.	↑
Khin, P. P. (2021)[48]	Dulaglutide s.c.	600 μg/kg/week for 4 weeks	Medium Medium	Diabetic sarcopenia in aged mice; Diabetic sarcopenia in young mice.	≈	In aged mice: ↑↑ (TA and QD muscles) In young mice: ≈	In both young and aged mice↑↑ Yang < aged	Both young and aged mice↑↑
Fan, D. M. (2023)[39]	Liraglutide s.c.	250 μg/kg/d for 8 weeks	High	Diabetic muscle atrophy mice;	↓↓	skeletal muscle mass ↑↑↑	Not measured	↑↑
Gurjar, A. A. (2020)[55]	Liraglutide s.c.	Freeze-Injury: 200 μg/kg, b.i.d, for 12 h-4 days Denervation model: 200 μg/kg, b.i.d, for 3 or 7 days Dex-model: 200 μg/kg, b.i.d, for 14 days. OVX model:	High	Dex-induced muscle atrophy in rat;	Dex-model: ↓ Other models: Not mentioned	Dex-model: ↑ Other models: Not mentioned	Freeze injury model: ↑↑↑ Denervation model: ↑ (Toe spread score of the denervated limbs) Dex-model: Grip strength ↑↑, rotarod motor	Freeze injury model: ↑ Denervation model: ↑↑↑ Dex-model: ↑↑ OVX model: ↑

		300 μg/kg, q.d, for 12 weeks.					coordination ↑, wire hanging test ↑↑↑ OVX model: Not mentioned	
Xiang, J. (2023)[35]	Liraglutide and Semaglutide s.c.	Liraglutide: 400 μg/kg/d for 4 weeks; Semaglutide: 60 μg/kg/d for 4 weeks	High Medium	Liraglutide in obesity-induced muscle atrophy; Semaglutide in obesity-induced muscle atrophy	Liraglutide: ↓ (17.8%) Semaglutide: ↓ (20.1%.)	Liraglutide: ↑ Semaglutide: ↑	Liraglutide: grip strength ↑ four-limb suspension time↑ Semaglutide: grip strength ↑ four-limb suspension time↑	Liraglutide: ↑ Semaglutide: ↑
Xu, Q. (2025)[54]	Liraglutide i.p.	Liraglutide: 400 μg/kg/d for 8 weeks	High	Diabetic SD rat;	Not mentioned.	↑	Not mentioned.	↑
Kamiya, M. (2022)[46]	PF1801 (Froniglutide) s.c.	Prophylactic treatment of CIM for 14 days (0-14): PF1801 5.0 mg/kg/day, PSL 20 mg/kg, PF1801 5.0 mg/kg/day + PSL 20 mg/kg. Therapeutic treatment of CIM for 14 days (7-21): PF1801 5.0 mg/kg/day, PSL 20 mg/kg, PF1801 5.0/2.5 mg/kg/day + PSL 20 mg/kg	High High High High High	Prophylactic treatment of CIM in mice with: PF1801 5.0 mg. PF1801 5.0 mg + PSL 20 mg. Therapeutic treatment of CIM in mice with: PF1801 5.0 mg; PF1801 5.0mg + PSL 20 mg; PF1801 2.5 mg + PSL 20 mg/kg;	Prophylactic treatment of CIM in mice with: PF1801 5.0 mg/kg/day: ≈ PF1801 5.0 mg/kg/day + PSL 20 mg/kg: ↓↓ Therapeutic treatment of CIM in mice with: PF1801 5.0 mg/kg/day: ≈ PF1801 5.0 mg/kg/day + PSL 20 mg/kg: ↓↓ PF1801 2.5 mg/kg/day + PSL 20 mg/kg: ↓↓	Prophylactic treatment of CIM in mice with: PF1801 5.0 mg/kg/day: ≈ PF1801 5.0 mg/kg/day + PSL 20 mg/kg: ↑↑ Therapeutic treatment of CIM in mice with: PF1801 5.0 mg/kg/day: ≈ PF1801 5.0 mg/kg/day + PSL 20 mg/kg: ≈ PF1801 2.5 mg/kg/day + PSL 20 mg/kg: ≈	Prophylactic treatment of CIM in mice with: PF1801 5.0 mg/kg/day: ↑↑ PF1801 5.0 mg/kg/day + PSL 20 mg/kg: ↑↑ Therapeutic treatment of CIM in mice with: PF1801 5.0 mg/kg/day: ↑↑ PF1801 5.0 mg/kg/day + PSL 20 mg/kg: ↑↑ PF1801 2.5 mg/kg/day + PSL 20 mg/kg: ↑↑	Prophylactic treatment of CIM in mice with: PF1801 5.0 mg/kg/day: ↑ PF1801 5.0 mg/kg/day + PSL 20 mg/kg: ↑↑ Therapeutic treatment of CIM in mice with: PF1801 5.0 mg/kg/day: ↑ PF1801 5.0 mg/kg/day + PSL 20 mg/kg: ↑↑ PF1801 2.5 mg/kg/day + PSL 20 mg/kg: ≈

Meaning of the abbreviations and symbols in the tables: Dex: Dexamethasone; Dex model: Dexamethasone-induced muscle atrophy model, mdx model: Duchenne muscular dystrophy model, CKD: Chronic Kidney Disease, CLD: chronic liver disease, CIM: C protein-induced myositis; PSL: prednisolone;↑↑: significantly increased,↑increased or enhanced or recovered, ≈: generally no change,↓: reduced or decreased,↓↓: significantly reduced or decreased, ≈: $P > 0.05$, ↑or↓：$P < 0.05$，↑↑ or ↓↓：$P < 0.01$，↓↓↓ or ↑↑↑: $P < 0.005$, ↓↓↓↓ or ↑↑↑↑: $P < 0.0001$.

Furthermore, the reports of increased phosphorylation of AKT, GSK3β, and FoxO1 by Gurjar et al. [55] further support the role of GLP-1RAs in maintaining mitochondrial integrity and promoting metabolic adaptation. Additionally, Nguyen et al. [52] found that Hsp72 is upregulated by AMPK (potentially through SIRT1), contributing to protein homeostasis and stress resistance. Moreover, Xiang et al. [35] demonstrated that SIRT1 plays a critical role in mitigating obesity-induced skeletal muscle atrophy. Specifically, SIRT1 activation suppresses the expression of muscle-specific ubiquitin ligases Atrogin-1 and MuRF-1, promotes myogenic differentiation by upregulating MyoD and Myogenin, and enhances insulin signaling through increased GLUT4 expression. Importantly, pharmacological inhibition of SIRT1 with the selective SIRT1 inhibitor EX-527 significantly attenuated the beneficial effects of GLP-1RAs on skeletal muscle integrity, thereby reinforcing the pivotal role of SIRT1 in this therapeutic context. However, Huang et al. [42] demonstrated that continuous GLP-1 treatment (100 ng/mL) during myogenic differentiation disrupts mitochondrial dynamics by suppressing kinesin-1 motor activity. This inhibition restricts mitochondrial movement toward the cell periphery and impairs their dispersion, leading to reduced basal respiration and ATP production, and ultimately contributes to compromised myogenic differentiation.

Table 6. Mechanistic insights into the GLP-1Ras.

Article ID	Drug administration method and animal model	Overall effect	Effect on muscle and body metabolic function	Effect on mitochondria	Oxidative stress and antioxidant response	Effect on the Ubiquitin-proteasome system	Effect on inflammation and necroptosis
Kamiya, M. 2022 [46]	PF1801, 5 mg/kg/day s.c. in myositis mice; C2C12 *in vitro*	↓ muscle necroptosis, ROS and inflammation; ↑ antioxidant response and grip strength.	↑ Grip strength, ↑ muscle CSA	↑ AMPK, ↓ PGAM5, ↑ antioxidant genes	↓ ROS, ↑ antioxidant genes (Nfe2l2, Hmox1, Nqo1, and Gclm)	↓ PGAM5 degradation via UPS	↓ FASLG-mediated muscle fiber necroptosis, ↓ TNFα, IL-6, HMGB1;
Hong, Y. 2019 [32]	Exendin-4 (100 ng/day i.p.), Dulaglutide (1 mg/kg/week s.c.) in muscle atrophy mice	↓ muscle atrophy (MSTN-NF-κB and GR-mediated catabolic signaling) and inflammation; ↑ muscle regeneration via PKA/AKT and myogenic transcription factors	↑ Muscle mass and function; ↓ MSTN, NF-KB, GR ((HSP70, HSP90, FKBP52, and p23)); ↑ PKA/AKT, MyoD/MyoG	↑ PGC-1α, mtTFA	Not mentioned	↓ MSTN-Atrogin-1, MuRF-1	↓ NF-κB
Iwai, S. 2023 [51]	Semaglutide (3 nmol/kg, s.c. every 3 days) in diabetic mice	↓ muscle atrophy (↓ ROS, inflammation, GCN2/eIF2α/ATF4 and NF-κB/MSTN/UPS signaling); ↑ mitochondrial biogenesis and myogenesis (activating GLP-1R/cAMP/PKA/AKT pathways)	↑ Muscle mass, grip strength, IGF-1; ↓ GCN2/eIF2α/ATF4, Sestrin2 expression and NF-κB/MSTN; ↑ mTORC1 activity and p70S6K phosphorylation, MyoD, MyoG	↑ PGC-1α, mtTFA, SIRT1, GLP-1R/cAMP/PKA/AKT pathways;	↓ hepatic and muscular ROS (e.g., 4-HNE), oxidative stress; ↑ antioxidant gene expression (Hmox1, Nqo1, Gstm3)	↓ Atrogin-1, MuRF-1, MSTN;	↓ NF-κB, IL-6, TNF-α
Khin, P. P. 2021 [48]	Dulaglutide (600 µg/kg/week s.c.) in aged mice	↓Sarcopenia (↑ mitochondrial function via ↑ OPA-1- ↓TLR-9-mediated NF-κB, IL-6, TNF-α, MuRF1, Atrogin-1, Myostatin and ↑ myogenic factors.	↑ Muscle mass, strength; ↑ MyoD, MyoG; ↓ Myostatin.	↑ PGC-1α, OPA-1	Not mentioned	↓ Atrogin-1, MuRF-1	↓ NF-κB,IL-6, TNF-α via TLR-9
Xu, Q. 2025 [54]	Liraglutide (0.4 mg/kg/day i.p.) in diabetic rats	↓muscle atrophy, cellular senescence and Sarcopenia (↑ YAP/TAZ pathway- ↓ P53/ P21-mediated cellular senescence and ↑ Cyclin D1 expression, myogenesis and muscle maintenance).	↑ Muscle mass; ↑ YAP/TAZ signaling pathway, Cyclin D1 expression; ↓ P53/ P21	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Gurjar, A. A.r 2020 [55]	Liraglutide (200–300 µg/kg s.c. b.i.d.) in multiple models	↑muscle regeneration, ↓ muscle atrophy and proteolysis (↑ GLP-1R–cAMP mediated PKA/CREB and EPAC/ PI3K/ AKT pathways, p38 MAPK and ERK1/2 signaling and phosphorylation of CREB, FoxO1, GSK3β, and mTORC1 downstream targets; ↑myogenesis ↓atrogenes)	↑ ↑ GLP-1R–cAMP mediated PKA/CREB and EPAC/PI3K/AKT pathways, p38 MAPK and ERK1/2 signaling; MyoD/Myogenin; ↓ Myostatin	↑ phosphorylation of AKT, GSK3β and FoxO1	Not mentioned	↓ Atrogin-1, MuRF-1;	↓ inflammation (↑ phosphorylation levels of CREB and AKT)
Nguyen, T. T. N. 2020[52]	Dulaglutide (600 µg/kg s.c.) in disuse model	↓ muscle atrophy (activating AMPK signaling to upregulate Hsp72 expression, which in turn inhibits NF-κB-mediated inflammation and caspase-dependent apoptosis, while downregulating atrogenes (MuRF1, Atrogin-1, Myostatin) and enhancing myogenic markers (MHC isoforms).	↑ Muscle strength, MHC isoforms, CSA, ↓ Myostatin;	↑ Hsp72 via AMPK	Not mentioned	↓ Atrogin-1, MuRF-1;	↑ AMPK/ Hsp72 expression, IκBα; ↓ TNFα, IL-1β, IL-6, NF-κB (p50), Caspase-3, cleaved PARP, Bax;
Xiang, J. 2023[35]	Liraglutide (400 µg/kg/day) & Semaglutide (60 µg/kg/day) s.c. in obese muscle atrophy mice	↓ muscle atrophy (↑SIRT1 pathway, GLUT4 expression, MyoD, Myogenin, insulin sensitivity and lipid metabolism and ↓Atrogin-1).	↑ Muscle mass, strength; ↑ SIRT1 pathway, GLUT4 expression, MyoD, Myogenin, insulin sensitivity and lipid metabolism; ↓ lipid infiltration, insulin resistance;	↑ SIRT1 pathway	Not mentioned	↓ Atrogin-1, MuRF-1;	Not mentioned

Meaning of the arrows in the table: ↑ increase/improve or upregulate; ↓ decrease/inhibit or downregulate. Not mentioned: Not given relevant information.
Abbreviations: CSA, cross-sectional area; UPS, ubiquitin–proteasome system; AMPK, AMP-activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; MSTN, myostatin; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; mtTFA, mitochondrial transcription factor A; ROS, reactive oxygen species; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; Hsp72, heat shock protein 72; CREB, cAMP response element-binding protein; FoxO1, forkhead box protein O1; GSK3β, glycogen synthase kinase 3 beta; MyoD/MyoG, myogenic differentiation/myogenin. Gene

symbols follow standard nomenclatureMeaning of the arrows in the table: ↑ increase/improve or upregulate; ↓ decrease/inhibit or downregulate. Not mentioned: Not given relevant information.

GLP-1RAs alleviate oxidative stress by enhancing antioxidant defense

Oxidative stress is a key pathogenic factor in the pathological process of muscle atrophy and mitochondrial dysfunction. Under oxidative stress, various factors, including FASL and H_2O_2, could increase reactive oxygen species (ROS) levels and lead to mitochondrial dysfunction in cells. Kamiya et al. [46] found that GLP-1RA can enhance the antioxidative ability of cells, effectively eliminating excessive ROS, and alleviating oxidative stress. This is achieved through the upregulation of antioxidative genes such as Nfe2l2, Hmox1, Nqo1, Gclm and Gstm3 via AMPK activation. Additionally, Iwai et al. [51] reported that GLP-RA significantly reduced ROS levels, including the expression of the lipid peroxidation product 4-HNE, in the liver and skeletal muscle tissues. They also upregulated the expression of antioxidative genes, including Hmox1, Nqo1, and Gstm3, thereby enhancing the cellular antioxidant response and protecting tissues from oxidative damage.

GLP-1RAs suppress muscle atrophy via inhibition of the ubiquitin-proteasome system (UPS)

As the main intracellular protein degradation mechanism, UPS plays a core regulatory role during the occurrence and development of sarcopenia and muscle atrophy. The 7 articles within the studies found that GLP-1RAs significantly downregulated muscle atrophy-related genes, including growth inhibitory factor MSTN (myostatin), ubiquitin-protein ligases atrogin-1 and MuRF-1 [32, 35, 46, 48, 51, 52, 55] by activating signaling pathways such as AMPK, GLP-1R/cAMP/PKA/AKT, p38 MAPK, and ERK1/2. Additionally, Kamiya et al. [46] found that GLP-RAs promoted the degradation of the mitochondrial phosphatase PGAM5 primarily through the UPS and inhibited mitochondrial lysis and necroptosis induced by PGAM5, thus helping to maintain the stability of mitochondrial structure and function.

GLP-1RAs inhibit inflammatory and necroptotic pathways in muscle atrophy

Inflammatory responses and necroptosis are considered key pathogenic factors in the development of muscle atrophy and sarcopenia. Six out of 8 articles reported inflammatory and necroptosis-related mechanisms of GLP-1RAs. Kamiya et al. [46] found that FASLG-mediated necroptosis of muscle fibers resulted in the release of various inflammatory markers such as TNF-α, IL-6, and HMGB1, which further aggravated muscle damage and functional loss. Meanwhile, GLP-1RAs downregulated inflammatory and stress pathways, including the NF-GCN2/eIF2α/ATF4 [51] and NF-κB pathway mediated by TLR-9 [48], reducing the expression of inflammatory markers like IL-6, TNF-α. Besides, activation of the AMPK signaling pathway could induce Hsp72 expression [52], which inhibited NF-κB-mediated inflammatory responses and caspase-dependent apoptosis (such as Caspase-3, cleaved PARP, Bax, etc.), thus alleviating muscle damage. Hsp72 also enhanced the expression of IκBα [52], stabilizing the inhibitory state of NF-κB, synergistically downregulating inflammatory factors such as TNF-α, IL-1β, IL-6 and maintaining immune-homeostasis of muscle tissue. Additionally, research by Gurjar et al. [55] indicated that GLP-1RAs inhibited inflammation by enhancing the phosphorylation of CREB and AKT through the activation of the GLP-1R–cAMP-mediated PKA-/CREB and EPAC/PI3K/AKT signaling pathways. They also reported that GLP-1RA upregulated the phosphorylation of downstream targets of p38 MAPK, ERK1/2, FoxO1, GSK3β, and mTORC1, inhibited necroptosis, and collectively promoted muscle regeneration while reducing muscle atrophy [55].

Effects of GLP-1RAs in clinical studies

For 8 clinical studies (shown in Table 7), 5 of them did not use external GLP-1RAs and only measured GLP-1 levels in the human body [46-48, 51, 52]. Although one clinical study used GLP-1RAs to treat diabetes or obesity induced sarcopenia, the dosage (3000 μg/day [49]) was significantly different from animal experiments. Another study simultaneously used glargine with GLP-1RA but did not specify the dosages [50]. Most of the studies indicate that elevated endogenous GLP-1 levels or exogenous GLP-1RA use are consistently associated with reductions in body weight and fat mass [40-45, 58]. However, only three studies—two involving GLP-1RAs and one assessing endogenous GLP-1—showed an increase in skeletal muscle mass (consistent with SMI) [39, 41, 45] or fat-free mass, whereas three studies without GLP-1RAs reported a decrease under high GLP-1 levels [40, 42, 44]. Notably, Huang et al. [42, 44] and Tacke et al. [43] measured GLP-1 levels in individuals with and without sarcopenia and found that sarcopenic individuals exhibited significantly higher GLP-1 levels compared to non-sarcopenic counterparts, along with lower body weight ($p = 0.003$) and muscle mass ($p = 0.015$). Additionally, Wandrag et al. [40] reported a

significant correlation between increased GLP-1 levels and decreased fat-free mass ($r = -0.47$, $p < 0.001$) during weight loss in a high-altitude hypoxic environment, suggesting a potential role of GLP-1 in muscle loss mechanisms.

Table 7. Characteristics of included clinical studies.

Literature ID	Total body muscle mass	Body weight	Skeletal muscle mass /FFM (Fat-free mass)	Fat mass	SMI	Appetite /food intake	GLP-1 levels	BMI
Osaka, T. (2023) [45]	Not reported (inferred ↑)	↓ (slight decrease-0.03 kg)	↑ (+0.78 kg, p = 0.013)	↓ (-0.87 kg, p = 0.022)	↑	≈	GLP-1RA (iGlarLixi)	≈
Perna, S. (2016) [41]	≈	↓ (-2.0 kg)	↑ (SMI +0.03 kg/m²)	↓ (-1.5 kg)	↑	≈	GLP-1RA (Liraglutide)	↓ (-0.78 kg/m²)
Ren Q, (2025) [58]	↓	↓	↓	↓	ASMI ↓ P<0.001	Not reported	GLP-1RA (Semaglutide)	↓ P<0.001
Huang, H. H. (2022) [44]	↓	↓ p = 0.003	↓ p = 0.015	↓ p = 0.013	not mentioned	Not reported (inferred ↓)	↑ (endogenous GLP-1 ↑ 1125.7 vs. 835.2 pg/mL, p = 0.023)	↓ p = 0.001
Wandrag, L. (2017) [40]	↓ (FFM)	↓ (-7.3 kg, p < 0.001)	↓ (4.0 ± 2.3 kg, p < 0.001)	↓ (3.3 ± 1.9 kg, p < 0.001)	not mentioned	Not reported (inferred ↓)	↑ (GLP-1 correlated with FFM loss, r = -0.47, p < 0.001) GLP-1 level was significantly negatively correlated with the decrease in FFM	Not reported (inferred ↓)
Tacke, M. (2013)[43]	↓ (FFM)	↓ (sarcopenia: non-sarcopenia = 76.7 ± 16.0 kg:88.4 ± 6.6 kg, p = 0.0003)	↓ (sarcopenia: 50.1 ± 6.5 kg Non-sarcopenia: 55.6 ± 10.9 kg p = 0.005)	↓ (sarcopenia: 22.5 ± 10.2 kg non-sarcopenia: 29.8 ± 9.6 kg p = 0.0001)	↓ (SMI)	Not reported	GLP-1 not significantly correlated with REE (p = 0.49)	↓
Huang, Hsien-Hao (2024) [42]	↓	↓ (sarcopenia : non-sarcopenia = 53.9 ± 1.2 k: 65.8 ± 1.6 kg, p = 0.001)	↓ (sarcopenia : non-sarcopenia = 18.4 ± 0.4 k: 23.6 ± 0.6 kg, P < 0.001)	↓ (sarcopenia : non-sarcopenia = 18.1 ± 0.9 kg: 21.8 ± 1.3 kg, p = 0.017)	↓ (GLP-1 inhibits muscle fusion)	↓ (GLP-1 inhibits GLUT4 transport)	↑ (endogenous GLP-1↑ 1021.5 ± 313.5 pg/mL vs 351.1 ± 39.0 pg/mL (P<0.05))	↓ (sarcopenia: non-sarcopenia = 25.7 ± 0.6: 22.0 ± 0.4, p < 0.001)
Fan, D. M. (2023) [39]	Not reported	Not reported	↑ (SMI)	Not reported	↑ (Experiment group: 6.3 ± 0.5 kg/m²; Control group: 7.5 ± 0.38 kg/m²)	Not reported	↑ (Experiment group: 0.3 ± 0.22 ng/mL; Control group: 0.5 ± 0.20 ng/mL. Endogenous GLP-1 ↑positively correlated with SMI, β = 0.435, p = 0.001)	≈ (Experiment group: 23.7 ± 2.87 kg/m²; Control group: 24.8 ± 1.40 kg/m²)

Abbreviations: ↑ increase/improve or upregulate; ↓ decrease/ inhibit or downregulate. ≈ No obvious change; All p values are from the original article, and all p values are shown in this table unless not given in the article.
Note: Fan et al., 2023 was an observational study comparing endogenous GLP-1 levels between patients with low skeletal muscle index (SMI < 7 kg/m²) and those with normal SMI (≥ 7 kg/m²)

Overall, GLP-1RAs are primarily prescribed for metabolic disorders such as diabetes and obesity, and their direct application in sarcopenia-specific populations remains rare. Most included studies focused on metabolic outcomes and only indirectly assessed muscle-related changes. Consequently, the number of eligible studies was limited, and substantial heterogeneity existed in study design, dosage, endpoints, and populations, restricting comparability and reducing clinical relevance. To provide a quantitative synthesis despite these limitations, we performed a meta-analysis of two studies reporting skeletal muscle index (SMI) at baseline and end-of-treatment. The pooled standardized mean difference (SMD) was –0.33 [95% CI: –0.51, –0.14], favoring end-of-study values, with low heterogeneity ($I^2 = 6\%$) (Supplementary Fig. 1). This finding suggests that, although evidence is limited, GLP-1RA treatment may be associated with a modest reduction in SMI, highlighting

the need for further research in sarcopenia-specific populations.

DISCUSSION

Since GLP-1RAs were originally developed for diabetes treatment, no standardized guidelines exist for their application in skeletal muscle disorders such as sarcopenia and muscle atrophy [59]. Therefore, determining appropriate dosing and treatment duration in preclinical models is essential.

In murine studies, GLP-1RA dosages are commonly calculated using the body surface area (BSA) method to translate human doses to animal equivalents, as recommended by the FDA (mouse dose in mg/kg = human dose in mg/kg × 12.3) [60]. This conversion accounts for interspecies differences in metabolic rate and body surface area, providing a more physiologically relevant dosing strategy. However, it is important to note that mice exhibit significantly faster drug metabolism and clearance compared to humans. For instance, the half-life of Semaglutide in mice is approximately 7.5 hours, whereas in humans it can reach up to 183 hours [61]. As a result, even when using human-equivalent doses (e.g., 0.6–3.0 mg/day), the actual in vivo drug exposure in mice may be insufficient to elicit comparable pharmacological effects. This necessitates the use of higher dosages or more frequent administration in murine models to maintain therapeutic efficacy [62].

Regarding a safe dosage for treating skeletal muscle atrophy or sarcopenia without inducing muscle loss, only two studies [46, 48] reported no significant change in skeletal muscle mass in experimental animals, whereas the majority—ten studies [32, 35, 39, 46–48, 50–52, 54, 55]—demonstrated a notable increase. Notably, some studies focusing on weight loss have reported that Semaglutide reduces both body weight and lean body mass in obese murine models without sarcopenia [57, 63]. Conversely, other studies have shown that body weight and food intake remain stable, even at higher dosages (Liraglutide 500 μg/kg/day for 4 months) in sarcopenic mouse models (SAMP8 mice) [67]. Combined with the previously discussed dosage-specific outcomes, these findings suggest that GLP-1RAs generally do not induce skeletal muscle loss under most sarcopenic or muscle atrophy conditions investigated in preclinical research.

It is well established that estrogen plays a critical role in skeletal muscle metabolism, mitochondrial function, and overall musculoskeletal health. Its sharp decline after menopause accelerates muscle wasting and alters bone–muscle crosstalk through cytokines such as interleukin-6, irisin, osteocalcin, and sclerostin, contributing to sarcopenia and osteoporosis [63, 64]. Estrogen also influences mitochondrial bioenergetics and ATP production, which are essential for muscle strength and endurance, making its deficiency a key factor in postmenopausal sarcopenia [64]. Despite this, most preclinical studies have relied on male mice, neglecting the majority of patients affected by sarcopenia and overlooking potential interactions between GLP-1 signaling and estrogen. These interactions may modulate muscle metabolism and therapeutic response, leading to attenuated or exaggerated effects on muscle loss. Recent reviews also highlight a paucity of data on sex differences in GLP-1 biology and therapeutic effects, despite growing evidence of quantitative differences and estrogen interactions [65]. Furthermore, the use of diverse disease models—such as dexamethasone-induced muscle atrophy [32], CKD-related muscle wasting [32], Duchenne muscular dystrophy in DBA/2J-mdx mice [32], sarcopenic obesity in obese mice [47], disuse muscle atrophy [52], and multiple diabetic sarcopenia models [39, 48, 49] in both young and aged rodents—introduces substantial variability in experimental outcomes. Additional complexity arises from studies targeting obesity-induced muscle atrophy [35, 47] with GLP-1 analogs (Liraglutide, Semaglutide) and corticosteroid-induced myopathy treated with PF1801 and PSL combinations [46]. While these models provide valuable mechanistic insights into distinct pathways such as inflammation, metabolic dysfunction, and hormonal regulation, their heterogeneity complicates cross-study comparisons and limits extrapolation to human sarcopenia, which is multifactorial and influenced by age, sex, and comorbidities. This diversity, combined with differences in dosing regimens and animal characteristics, underscores the challenge of translating preclinical evidence into clinically actionable strategies.

All clinical trials included in our review consistently demonstrated body weight reduction, with five out of eight studies reporting a decrease in muscle mass [40, 42-44, 58]. However, the relationship between circulating GLP-1 levels and muscle weight appears inconsistent: one study observed a negative correlation in healthy individuals during high-intensity expeditions [40], whereas another reported a positive correlation in patients with diabetes [39], both with $P < 0.001$. These discrepancies suggest that GLP-1RAs may exert distinct effects depending on metabolic status, or that extreme physical activity (e.g., mountain climbing) may induce muscle catabolism beyond typical daily activity [40]. Although several clinical studies reported reductions in fat-free mass (lean mass) [40, 64, 65], these changes largely reflect overall weight loss rather than direct skeletal muscle loss [40, 64, 65]. Besides, lean mass includes all non-fat components, such as muscle, bone, organs, and fluids. While some degree of muscle mass reduction may occur during pharmacological weight loss,

such changes are generally considered acceptable if accompanied by preserved or improved muscle function, as indicated by measures such as increased grip strength [37, 66]. For instance, a single-center randomized trial found that Semaglutide (up to 1 mg/week) preserved lean body mass during weight loss in elderly individuals with obesity [68]. These findings suggest that modest reductions in muscle mass may represent normal adaptive responses to weight loss, particularly in aging populations [37]. Meanwhile, with economic development and rising living standards, many elderly individuals are overweight while simultaneously suffering from sarcopenia and osteoarthritis [66, 67].

Although some studies suggest that GLP-1RAs are generally safe [68], their safety profile in frail or sarcopenic populations warrants closer examination. Side effects such as malnutrition [69], which may result from excessive body weight loss, are of particular concern in older adults with reduced lean mass. This can exacerbate conditions like sarcopenia and sarcopenic obesity [69], potentially leading to further functional decline. In addition, hypoglycemia remains a notable risk, especially in individuals with impaired glucose regulation or reduced muscle mass [70]. Gastrointestinal (GI) side effects—including nausea, vomiting, diarrhea, and constipation—are frequently reported in clinical settings and may significantly impact treatment adherence and nutritional status [71]. These adverse effects should be carefully considered when establishing safe and tolerable dosing strategies for human use, particularly in vulnerable populations such as the elderly or those with muscle-wasting conditions. Since dosage varies depending on the specific GLP-1RA drug and its formulation, researchers should begin with the minimal effective dose and adjust based on the individual's response [72]. Although current data are insufficient to establish a conclusion between treatment duration and the efficacy of GLP-1RAs on sarcopenia, existing evidence suggests that longer durations and higher dosages tend to produce more pronounced weight loss effects [39, 47] compared to shorter durations and lower dosages [32, 52, 73].

The dosage of GLP-1RAs plays a crucial role in their effects on body weight, but the specific type of GLP-1RAs is also significant. While GLP-1RAs share core mechanisms, including enhancing glucose-dependent insulin secretion, inhibiting glucagon release, and delaying gastric emptying, they differ in their effectiveness for body weight reduction and glycemic control. These variations arise from various factors, such as molecular structure, pharmacokinetics, and target specificity. For example, Exendin-4, derived from the saliva of the Gila poisonous lizard, has relatively low homology with human GLP-1 (53%), a short half-life of approximately 2.4 hours, and a modest weight-loss effect (5-6%) due to its more rapid degradation by DPP-4 [74]. The half-life, stability, and receptor targeting of different GLP-1RAs have been enhanced through amino acid modifications and fatty acid chain conjugation (e.g., Liraglutide and Semaglutide), and IgG4 Fc fusion (e.g., Dulaglutide) [75, 76]. According to Chang et al., Semaglutide (considered the most effective) and Liraglutide demonstrated superior weight loss outcomes, whereas Dulaglutide showed greater efficacy in glycemic control in T2D [77-79]. Thus far, one study has investigated the use of Froniglutide (PF1801) [46] in the treatment of inflammatory polymyositis. Although data are limited, PF1801, a GLP-1RA encompassing a fused elastin-like peptide-120 to enhance half-life, did not induce weight loss or skeletal muscle loss when administered alone, even at a high dose of 5000 μg/kg/d. Instead, it was associated with increased grip strength and an enlargement of the CSA of skeletal muscle fibers. Intriguingly, Froniglutide was found to reduce body weight when combined with 20 mg/kg of prednisolone, a drug typically associated with weight gain when used alone. This unexpected outcome suggests the possibility of an unknown mechanism or a synergistic interaction between the two agents [46]. Consequently, Froniglutide may represent a promising therapeutic approach for muscle atrophy or sarcopenia, particularly in the context of myositis which is also characterized by muscle weakness and atrophy [80]. Notably, next-generation GLP-1 receptor agonists (GLP-1RAs), such as Tirzepatide and Retatrutide, employ a multi-target strategy by additionally acting on GIP and/or glucagon receptors (GIPR and GCGR) [81]. Through structural modifications, these agents have demonstrated enhanced efficacy in glycemic control, improved metabolic and cardiovascular outcomes, and substantial weight loss with greater preservation of lean mass [82]. According to recent evidence published in The Lancet [83], Tirzepatide—a dual GIP/GLP-1 receptor agonist and currently the most potent weight-loss agent in clinical use—has shown significant improvements in muscle composition. Specifically, it reduced muscle fat infiltration beyond population-based expectations while preserving muscle volume relative to weight loss. Furthermore, a clinical study involving adults with obesity or overweight reported that the proportion of weight lost as fat versus lean mass remained relatively consistent across clinically relevant subgroups [84]. These findings suggest that Tirzepatide can enhance body composition while preserving skeletal muscle, highlighting its therapeutic potential for improving both metabolic health and muscle quality.

Despite encouraging preclinical findings, the translational potential of GLP-1RAs for sarcopenia remains uncertain. Only eight clinical studies were

identified, most of which were observational or indirectly related to sarcopenia, and few trials explicitly targeted sarcopenic populations [39, 40, 64–70]. Considerable heterogeneity in study design, dosing regimens, and outcome measures further limits interpretation, highlighting the need for caution when extrapolating animal data to human applications in the context of sarcopenia. Therefore, clinical use of GLP-1RAs in sarcopenic or frail populations should be approached carefully, balancing metabolic benefits against potential risks of muscle loss. Future research should focus on dose optimization, combined interventions such as resistance training or protein supplementation, and long-term functional outcomes to clarify therapeutic potential in aging and disease contexts.

GLP-1RAs are known to interact with G-protein-coupled receptors (GPCR), which are categorized into three subtypes: β1 (primarily in the heart), β2 (found in the lungs, vascular smooth muscles and skeletal muscles) and β3 (located in adipose tissue). After GLP-1R activation, it couples with the Gs protein, leading to the generation of cAMP. This, in turn, activates protein kinase A (PKA), initiating a classical signaling cascade that influences cell growth, metabolism, muscle adaptation and anti-apoptotic related pathways [85, 86]. As shown in Table 6, the most relevant signaling pathway associated with GLP-1RA in skeletal muscle atrophy or sarcopenia is the GLP-1RA-cAMP/PKA/AKT pathway [32, 51, 55]. This pathway plays multiple roles, including the inhibition of catabolic processes by downregulating FoxO1 [55], myostatin [32, 48, 51], NF-κB [32, 51, 52] and atrogenes [32, 51, 55] such as MuRF1/Atrogin-1. It also promotes myogenesis by upregulating MyoD and Myogenin [32, 51, 52, 55]. Additionally, several secondary pathways have been reported to exert beneficial effects on sarcopenia, including AMPK/SIRT1 [52], YAP/TAZ [54], mitochondrial dynamics [32, 35, 46, 48, 51, 52, 55], the UPS [32, 35, 46, 48, 51, 52, 55], and SIRT1-independent pathway [35]. However, conflicting findings have emerged. Huang et al. [42] reported that elevated GLP-1 levels in individuals with sarcopenia inhibited myogenic differentiation and GLUT4 translocation via the GLP-1R-cAMP-PKA pathway, potentially through suppression of Kinesin-1 and interference with insulin signaling. Conversely, other studies have shown that GLP-1RAs such as exenatide and Liraglutide enhance glucose uptake and metabolic activity in skeletal muscle cells via the GLP-1R-AMPK signaling pathway [87]. These discrepancies highlight the need for further investigation to clarify the role of GLP-1R signaling in muscle physiology.

Another important functional pathway involves mitochondria-related mechanisms. Xiang et al. [35] and Nguyun et al. [52] reported that GLP-1RAs influence SIRT1 through UPS-mediated Atrogin-1, modulation of myogenic markers, and induction of Hsp72 via AMPK signaling, as well as enhanced GLUT4 expression. In parallel, Gurjar et al. [55] investigated the phosphorylation of key downstream targets such as CREB, FoxO1, GSK3β, and components of the mTORC1 pathway, which collectively contribute to protein synthesis and muscle regeneration. Furthermore, previous studies have identified SIRT1 [88] and FoxO1 [89, 90] as crucial regulators of mitochondrial dynamics. One study explored the role of SIRT1 in regulating mitochondrial function during aging [91], while others demonstrated that SIRT1 positively influences autophagy and mitochondrial activity in embryonic stem cells under oxidative stress [92]. Additionally, Wan et al. reported that SIRT1 contributes to the regulation of mitophagy in age-related diseases by integrating multiple pathways and factors, such as PGC-1α, FoxO1, the UPS, AMPK, and mTOR, with SIRT1 serving as a central mediator [93]. Interestingly, several studies have revealed crosstalk among these signaling pathways, particularly involving FoxO1, PGC-1α and SIRT1 [94]. For instance, GLP-1RAs have been shown to enhance muscle mass by inhibiting PI3K/AKT-mediated FoxO1 phosphorylation and suppressing Atrogin-1 activation [55]. They also regulate glucose and lipid metabolism, as well as muscle adaptation, through the cAMP/PKA-CREB-FoxO1 signaling pathway [95]. Similarly, elevated PGC-1α levels downregulate the transcription of Atrogin-1 and MuRF-1 via the SIRT1-PGC-1α-FoxO1 axis [35] and promote protein synthesis by activating mTORC1 through enhanced mitochondrial energy production [51]. Furthermore, PGC-1α reduces the levels of NF-κB, Myostatin, and Atrogin-1 levels through ROS-mediated mechanisms [48], while improving mitochondrial function by inhibiting the p53/p21 aging pathway [54]. These findings underscore the pivotal role of PGC-1α in mitochondrial biogenesis, energy metabolism and oxidative stress regulation [96-98]. Notably, Khin et al. found that Dulaglutide treatment inhibited the NF-κB pathway mediated by TLR-9 in muscle atrophy, resulting in reduced expression of inflammatory markers such as IL-6, TNF-α, and improved muscle mass [48]. Similarly, Wong et al. reported that GLP-1RA activation inhibits TLR-agonist-induced inflammation [99]. Additionally, Gurjar et al. [55] highlighted the involvement of the p38 MAPK pathway in the muscle regeneration and anti-proteolytic effects of GLP-1RAs. The p38 MAPK pathway plays a crucial role in various biological processes, including inflammatory signaling (TLR/NF-κB → TAK1 → MKK3/6 → p38 MAPK), muscle adaptation (cAMP/PKA → p38 MAPK → MEF-2), and apoptotic regulation (ASK1 → MKK3/6 → p38 MAPK → Stat1) [100-102]. Taken together, these findings

suggest that the therapeutic effects of GLP-1RAs on muscle atrophy may be partially mediated through anti-inflammatory mechanisms, suggesting their potential efficacy in the treatment of knee osteoarthritis. A simple illustration summarizing the main pathways and effects is shown in Figure 4.

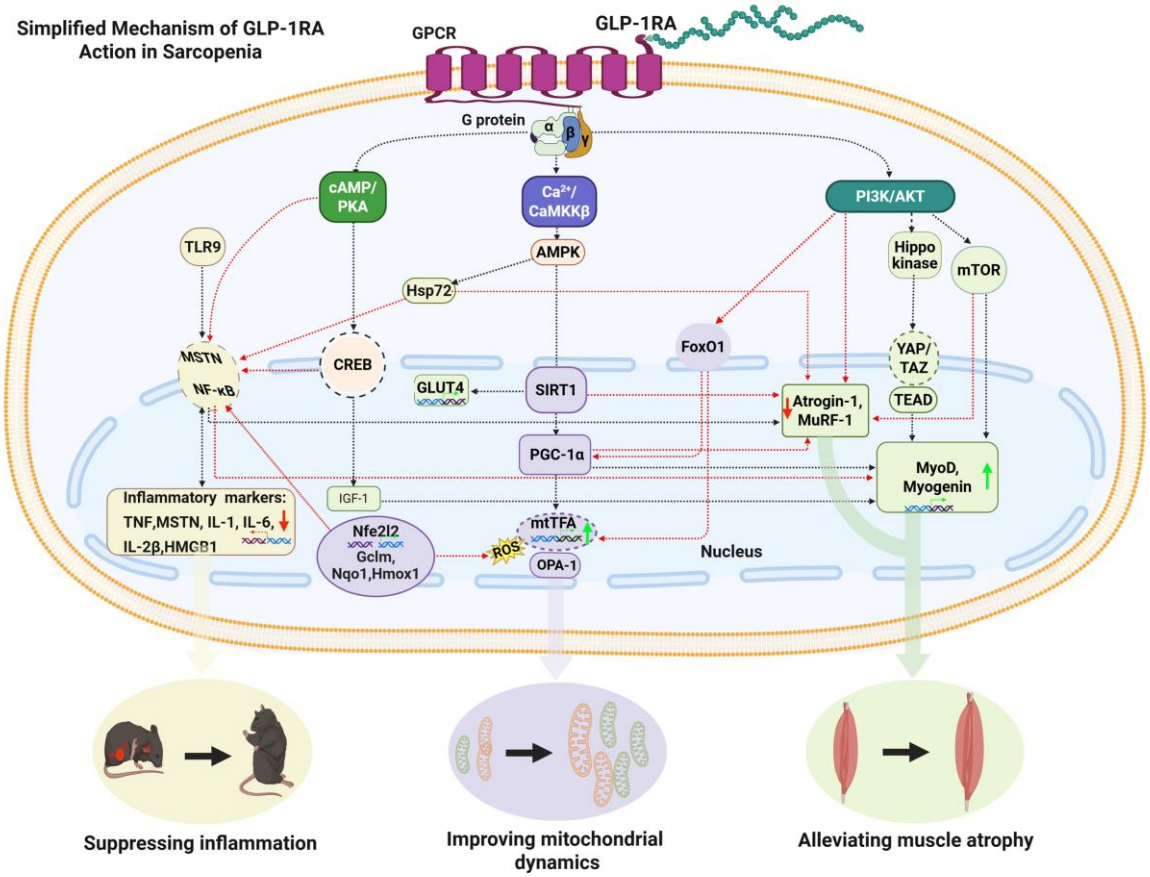

Figure 4. Schematic representation of the mechanisms by which GLP-1RAs influence skeletal muscle health, based on evidence from this systematic review and supporting literature. Black dashed arrows indicate promotion of biological processes, while red dashed arrows indicate inhibition. Dark green upward arrows represent upregulation of gene expression, and dark red downward arrows represent downregulation. The background colors of molecular components correspond to their associated biological processes: **light green (right)** indicates pathways related to skeletal muscle metabolism and hypertrophy, including IGF-1 signaling and activation of MyoD and Myogenin with suppression of Atrogin-1 and MuRF-1, thereby alleviating muscle atrophy through enhanced anabolic signaling and inhibition of catabolic pathways; **light purple (center)** denotes mitochondrial dynamics and biogenesis, showing upregulation of PGC-1α, mtTFA and SIRT1, promotion of mitochondrial biogenesis, and inhibition of ROS production and PGAM5 expression, which collectively improve mitochondrial function and antioxidant response; **light yellow (left)** corresponds to inflammation-related processes, highlighting downregulation of pro-inflammatory markers such as TNF-α, IL-6, IL-1β and HMGB1 and suppression of NF-κB signaling, contributing to reduced cytokine activity and necroptosis.

Given the widespread use of GLP-1 receptor agonists in diabetes and weight management, emerging concerns suggest they may exacerbate muscle loss in older adults with sarcopenia [103, 104]. A recent clinical case even reported Semaglutide-induced sarcopenia in an elderly individual with diabetes [105]. To mitigate these effects, some studies have explored combining GLP-1RAs with nutritional interventions, such as high-fat or high-protein diets, or anabolic agents like testosterone or ghrelin analogues [106-108]. We also propose several strategies in this context. A straightforward theory involves ensuring adequate protein intake alongside GLP-1RA therapy [109, 110]. For example, Memel et al. recommended a high-protein diet combined with resistance training as a tailored intervention to prevent muscle mass loss during GLP-1RA treatment in individuals with sarcopenia [104, 111]. Another strategy is to use combination therapies that stimulate appetite and promote weight gain. One study employed Bimagrumab, an activin type II receptor blocker that promotes muscle growth by inhibiting activin receptor signaling [57]. Similarly, BCL6, another activin type II receptor blocker,

has been shown to support muscle mass homeostasis under varying nutritional states. Additionally, blocking GDF8 (myostatin) and activin A has been found to prevent GLP-1RA-induced muscle loss while enhancing fat loss in obese male mice and non-human primates [112]. Another approach involves the use of ghrelin receptor agonists or multi-receptor agonists to stimulate food intake, enhance gastric motility, and increase gastric acid secretion [113]. Sjögren et al. used Anamorelin, a ghrelin receptor agonist, and reported that it effectively reversed skeletal muscle catabolism in an R6/2 mouse model of muscle atrophy [114]. Similarly, recent clinical evidence suggests that multi-receptor agonists such as Retatrutide may help preserve lean mass during weight loss, further supporting their potential role in maintaining muscle health [115]. Busquets et al. also reported that Megestrol acetate positively affects muscle protein metabolism and recommended it for cancer cachexia due to its appetite-stimulating and weight-gaining properties [116]. They offer valuable insights into the mechanistic understanding and clinical management of sarcopenia and related muscle-wasting disorders.

This review has several limitations. First, the included studies employed a wide range of GLP-1RA dosages, disease models, and experimental methodologies, resulting in heterogeneous effects on key parameters such as body weight and muscle mass. This variability complicates synthesis and limits the ability to draw consistent conclusions. Moreover, differences in animal age, sex, and dosing regimens raise concerns about external validity, including the frequent use of young, healthy male mice, which may not represent older adults with comorbidities—the primary population affected by muscle atrophy and sarcopenia. Second, the predominant use of male animal models meant that the influence of sex hormones on GLP-1RA responsiveness was not adequately investigated. This omission restricts applicability to older female populations, who are at higher risk of sarcopenia and may exhibit distinct physiological responses due to menopause-related hormonal changes. Third, the clinical studies reviewed did not account for several potentially influential factors—such as diabetes duration, smoking status, alcohol consumption, dietary habits, and exercise levels—that could confound the relationship between GLP-1RA use and sarcopenia or muscle wasting syndromes. Lastly, due to significant heterogeneity among the studies, a meta-analysis could not be performed. Consequently, this review provides preliminary insights rather than definitive clinical guidelines for the use of GLP-1RAs in treating muscle atrophy and sarcopenia.

In conclusion, many studies reported beneficial effects of GLP-1RAs on metabolism, mitochondrial function, inflammation, and skeletal muscle health. In murine sarcopenia and muscle atrophy models, their impact on body weight is dose-dependent: low doses (0.1–4.11 μg/kg/d) increase weight, medium doses (60–142.86 μg/kg/d) have a neutral effect on body weight, and high doses (250–5000 μg/kg/d) result in weight loss. Animal studies frequently describe improvements in muscle mass, grip strength, and CSA of muscle fibers, whereas human trials typically show weight loss and, in some cases, a reduction in muscle mass. Mechanistically, GLP-1RAs regulate myogenic and atrophy-related genes via signaling pathways including cAMP/PKA, AMPK-PGAM5, SIRT1-PGC-1α, and NF-κB/Myostatin, although most evidence remains correlative, warranting further validation.

However, it is important to note that most preclinical studies to date have been conducted in young male murine models, with limited representation of aged, female, or sarcopenic animals. This limits the translational relevance of the findings to the broader, more diverse human population affected by sarcopenia. Hence, low-dose GLP-1RAs may be explored for individuals in the early-stage of sarcopenia or obesity- and diabetes-induced sarcopenia without muscle loss, but are not advised for underweight individuals or those with advanced sarcopenia. To mitigate muscle loss, adequate protein intake, resistance exercise, and regular monitoring of muscle parameters are essential. Future studies should prioritize low-dose interventions in aged animal models, including both sexes, and focus on clinically relevant populations with sarcopenia and obesity to better elucidate mechanisms and enhance translational applicability.

Competing financial interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. All authors have reviewed and approved the author contributions listed below.

Authors' contributions

WHC conceived the idea and revised the manuscript; AM drafted the manuscript, prepared tables and figures, and revised the manuscript; RA and QJW contributed to the data extraction; CWW helped with meta-analysis; C C, TCYK conception and design of the work; SLC, RMYW, NZ, HK revised the manuscript.

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Supplementary Materials

The Supplementary data can be found online at: www.aginganddisease.org/EN/10.14336/AD.2025.1165.

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