NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ

JOURNAL OF EDUCATION, HEALTH AND SPORT
eISSN 2391-8306 · Open Access · Peer-reviewed
apcz.umk.pl/JEHS · Nicolaus Copernicus University in Toruń



PIECZARA, Szymon, MUSIAŁ, Paulina, NOWICKI, Wojciech, MACHAJ, Damian, STAŃKO, Mikołaj, STEFANIK, Zofia and URBANOWICZ, Piotr. Beyond Weight Loss: Pleiotropic Effects of GLP-1 Receptor Agonists — A Narrative Review.Journal of Education, Health and Sport. 2026;95:76671. https://doi.org/10.12775/JEHS.2026.95.76671

ARTICLE TIMELINE
Received: 13.10.2026.
Accepted: 10.11.2026.
Published: 18.11.2026.

INDEXING & EVALUATION
MEiN points: 40 Unique ID: 201159
Disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

The journal has been awarded 40 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32318). Unique Journal Identifier: 201159. Scientific disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

Punkty Ministerialne z 2019 – aktualny rok 40 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 L.p. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu). © The Authors 2026.

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Beyond Weight Loss: Pleiotropic Effects of GLP-1 Receptor Agonists — A Narrative Review

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Abstract

Introduction and purpose. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), including semaglutide and tirzepatide, were introduced for glycaemic control and weight reduction, but a rapidly expanding body of evidence shows benefits that extend far beyond the scale. The purpose of this narrative review is to synthesise current evidence on the pleiotropic effects of GLP-1 RAs across cardiovascular, renal, hepatic, respiratory, neurological and addiction-related domains, and to examine the impact of these agents on body composition and the role of physical activity in preserving skeletal muscle.

Description of the state of knowledge. Landmark randomised trials demonstrate reductions in major adverse cardiovascular events (SELECT, SUSTAIN-6, SOUL), slowed progression of chronic kidney disease (FLOW), resolution of metabolic dysfunction-associated

steatohepatitis (ESSENCE) and marked improvement in obstructive sleep apnoea (SURMOUNT-OSA). These effects are only partly explained by weight loss and glucose lowering, implicating direct anti-inflammatory and tissue-protective mechanisms. A key limitation is that roughly one quarter of total weight lost is lean mass; evidence indicates that resistance and combined exercise can substantially attenuate this loss and preserve physical function.

Summary. GLP-1 RAs have evolved into multi-organ cardiometabolic therapies. Combining pharmacotherapy with structured physical activity, particularly resistance training, appears essential to optimise the quality of weight loss and preserve muscle, linking pharmacology with exercise science.

Keywords: Glucagon-Like Peptide-1 Receptor Agonists; Semaglutide; Tirzepatide; Exercise; Body Composition; Cardiovascular Diseases

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Introduction and purpose

Obesity and type 2 diabetes mellitus (T2DM) are among the most pressing public-health challenges of the twenty-first century, driving cardiovascular disease, chronic kidney disease (CKD), liver disease and premature mortality [1,3]. The therapeutic landscape has been transformed by glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and the dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonist tirzepatide, agents that reduce body weight to a degree previously achievable only with bariatric surgery [1,5]. Once-weekly semaglutide 2.4 mg reduces body weight by approximately 15% at 68 weeks, and tirzepatide by up to 21% [5,72].

However, framing these medicines solely as weight-loss drugs understates their clinical reach. GLP-1 receptors are expressed in the pancreas, cardiovascular system, kidney, central nervous system and immune cells, providing a biological basis for effects on multiple organ systems [1,3]. Over the last five years, dedicated outcome trials have shown that GLP-1 RAs reduce cardiovascular events, slow kidney disease progression, resolve steatohepatitis, improve obstructive sleep apnoea and may influence neurodegenerative disease and addictive behaviours [3,4,14,18,36]. Critically, many of these benefits appear only partially attributable to weight loss or improved glycaemia, suggesting direct, pleiotropic mechanisms [40,42].

This expanding therapeutic role carries an important caveat relevant to health and sport sciences: a substantial proportion of the weight lost during GLP-1 RA therapy is lean (fat-free) mass [49,50,51]. Because skeletal muscle is central to metabolic health, physical function, glucose disposal and healthy ageing, the interaction between pharmacological weight loss and exercise has become a focus of intense clinical interest [55,57]. Understanding how physical activity can safeguard muscle during pharmacotherapy is directly relevant to practitioners in education, health and sport.

The purpose of this narrative review is therefore twofold: (1) to summarise the pleiotropic, "beyond weight loss" effects of GLP-1 RAs across organ systems, drawing on recent landmark randomised controlled trials and meta-analyses; and (2) to critically appraise the evidence on GLP-1 RA-associated changes in body composition and the role of physical activity, particularly resistance training, in preserving skeletal muscle mass and function.

Description of the state of knowledge

Pharmacological background and mechanisms

GLP-1 is an incretin hormone secreted by intestinal L-cells in response to nutrient intake. It enhances glucose-dependent insulin secretion, suppresses glucagon, slows gastric emptying and promotes satiety through central pathways [1,3]. Pharmacological GLP-1 RAs achieve supraphysiological receptor activation, producing durable glycaemic and weight benefits. Tirzepatide additionally activates the GIP receptor, which may contribute to its greater efficacy [3,9].

A central theme of contemporary research is that the benefits of these agents extend beyond metabolic improvement. Anti-inflammatory signalling is a leading candidate mechanism: GLP-1 RAs reduce high-sensitivity C-reactive protein (hsCRP) by approximately 30-38%, with reductions emerging within 4-8 weeks, before major weight loss, and occurring even among patients who do not lose weight [39,40]. In pooled analyses, weight and glucose changes explained only 20-60% of the reduction in inflammatory markers [40]. These observations support direct, weight-independent tissue effects that help explain the cardiovascular and renal benefits discussed below [40,42].

Cardiovascular effects

The cardiovascular evidence base for GLP-1 RAs is now among the strongest in cardiometabolic medicine. In the SELECT trial, 17,604 patients with obesity and established

atherosclerotic cardiovascular disease but without diabetes were randomised to semaglutide 2.4 mg weekly or placebo; semaglutide reduced the primary three-point major adverse cardiovascular event (MACE) composite by 20% (hazard ratio [HR] 0.80; 95% confidence interval [CI] 0.72-0.90; P<0.001) over a mean of 39.8 months [7]. All-cause mortality favoured semaglutide (HR 0.81; 95% CI 0.71-0.93), and the MACE benefit emerged early, before maximal weight loss [7]. In a prespecified heart-failure subgroup, benefits were at least as large, including in patients with heart failure with preserved ejection fraction (HFpEF) [14].

Earlier trials in T2DM established the class effect. SUSTAIN-6 showed a 26% MACE reduction with subcutaneous semaglutide (HR 0.74; 95% CI 0.58-0.95), driven in part by a 39% reduction in nonfatal stroke [15,16]. LEADER demonstrated that liraglutide reduced cardiovascular death (HR 0.78) and all-cause mortality (HR 0.85) [1,3]. The SOUL trial extended these findings to oral semaglutide 14 mg in 9,650 patients with T2DM and atherosclerotic disease or CKD, demonstrating a 14% MACE reduction (HR 0.86; 95% CI 0.77-0.96; P=0.006), driven predominantly by a reduction in myocardial infarction [8].

For tirzepatide, SURPASS-CVOT compared it head-to-head against dulaglutide (an active comparator with proven cardiovascular benefit) in 13,299 patients with T2DM and established disease. Tirzepatide met noninferiority for MACE (HR 0.92; 95% CI 0.83-1.01; P=0.003 for noninferiority) and significantly reduced all-cause mortality by 16% (HR 0.84; 95% CI 0.75-0.94), although superiority over dulaglutide for MACE was narrowly missed (P=0.09) [9]. A prespecified imputed-placebo analysis estimated a MACE HR of 0.72 (95% CI 0.55-0.94) versus placebo [10]. In HFpEF with obesity, the SUMMIT trial randomised 731 patients to tirzepatide or placebo and reported a 38% reduction in the composite of cardiovascular death or worsening heart failure (HR 0.62; 95% CI 0.41-0.95; P=0.026), with clinically meaningful improvements in symptoms and six-minute walk distance [11]. These findings complement the STEP-HFpEF programme, in which semaglutide improved heart-failure symptoms, reduced inflammation and decreased heart-failure events in obesity-related HFpEF [12,13]. The 2025 American College of Cardiology scientific statement nonetheless cautions that the SUMMIT event count was small [4].

Table 1 summarises the principal cardiovascular outcome trials.

Table 1. Cardiovascular outcome trials of GLP-1 receptor agonists and tirzepatide.

Trial (year)	Agent	Population	N	Primary MACE HR (95% CI)	All-cause mortality HR	Reference
SUSTAIN-6 (2016)	SC semaglutide	T2DM, high CV risk	3,297	0.74 (0.58-0.95)	0.81 (0.61-1.08)	[15,16]
SELECT (2023)	SC semaglutide 2.4 mg	Obesity + ASCVD, no DM	17,604	0.80 (0.72-0.90)	0.81 (0.71-0.93)	[7]
SOUL (2025)	Oral semaglutide 14 mg	T2DM + ASCVD/CKD	9,650	0.86 (0.77-0.96)	Not formally tested	[8]
SURPASS-CVOT (2025)	Tirzepatide vs dulaglutide	T2DM + ASCVD	13,299	0.92 (0.83-1.01)*	0.84 (0.75-0.94)	[9]
SUMMIT (2025)	Tirzepatide	HFpEF + obesity	731	CV death/worsening HF: 0.62 (0.41-0.95)	1.25 (0.63-2.45)	[11]

*Noninferiority vs. active comparator dulaglutide met; superiority not met. ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction.

Renal effects

The FLOW trial was the first dedicated kidney-outcome trial of a GLP-1 RA. It randomised 3,533 patients with T2DM and CKD to semaglutide 1.0 mg weekly or placebo and was stopped early for efficacy [18]. Semaglutide reduced the primary composite of major kidney

events (kidney failure, ≥50% eGFR decline, kidney death or cardiovascular death) by 24% (HR 0.76; 95% CI 0.66-0.88; P=0.0003), with a number needed to treat over three years of about 20 [18]. Semaglutide also slowed the annual rate of eGFR decline by approximately one third (estimated treatment difference +1.16 mL/min/1.73 m²/year) and reduced all-cause mortality by 20% (HR 0.80; 95% CI 0.67-0.95) [18]. Benefits were consistent across CKD severity and appeared additive to sodium-glucose cotransporter-2 (SGLT2) inhibitors [19,20].

Prior to FLOW, renal benefits were documented as secondary endpoints in cardiovascular trials: liraglutide (LEADER) reduced a renal composite by 22% [22], and pooled SUSTAIN-6/LEADER analyses showed reduced albuminuria and slowed eGFR decline [26]. A prespecified pooled analysis of SELECT, FLOW and SOUL (30,787 participants) confirmed a 16% reduction in the kidney composite (HR 0.84; 95% CI 0.77-0.91) [27]. Short-term data from the SMART trial suggest a 52% reduction in urinary albumin-to-creatinine ratio even in overweight or obese patients with CKD without diabetes [30]. Mechanistically, renal protection appears largely independent of glucose lowering, mediated by anti-inflammatory, anti-oxidant and anti-fibrotic actions, with glycaemia and blood pressure changes explaining only 10-25% of the benefit [31]. Based on FLOW, semaglutide received regulatory approval to reduce kidney disease progression in T2DM with CKD, and current KDIGO and ADA-KDIGO guidance endorse GLP-1 RAs in this setting [21,28,29].

Table 2. Key renal outcome data for GLP-1 receptor agonists.

Trial (year)	**Agent**	**Population**	**Kidney composite HR (95% CI)**	**Reference**
FLOW (2024)	Semaglutide 1.0 mg	T2DM + CKD	0.76 (0.66-0.88)	[18]
LEADER (2017)	Liraglutide	T2DM + high CV risk	0.78 (0.67-0.92)	[22]
SELECT kidney (2024)	Semaglutide 2.4 mg	Obesity + ASCVD, no DM	0.78 (0.63-0.96)	[25]
Pooled	Semaglutide	Mixed	0.84 (0.77-	[27]

SELECT/FLOW/SOUL (2026)			0.91)	

Hepatic effects: metabolic dysfunction-associated steatohepatitis

Metabolic dysfunction-associated steatohepatitis (MASH) is a leading cause of cirrhosis and has no historically effective pharmacotherapy. In the phase 3 ESSENCE trial, 800 adults with biopsy-confirmed MASH and stage F2-F3 fibrosis were randomised to semaglutide 2.4 mg weekly or placebo [32]. Both co-primary endpoints were met: MASH resolution without worsening fibrosis occurred in 62.9% versus 34.3% (difference 28.7 percentage points; P<0.001), and fibrosis improvement without worsening MASH in 36.8% versus 22.4% (difference 14.4 percentage points; P<0.001) [32]. Improvements in noninvasive markers were apparent by week 12 [32]. These results underpinned accelerated regulatory approval and updated AASLD practice guidance recommending noninvasive tests for patient selection [33,34]. Preclinical work indicates both weight-dependent and weight-independent anti-fibrotic mechanisms despite the absence of hepatic GLP-1 receptors [35].

Obstructive sleep apnoea

In the SURMOUNT-OSA trials, tirzepatide was evaluated in 469 adults with moderate-to-severe obstructive sleep apnoea (OSA) and obesity, both with and without positive airway pressure therapy [36]. Tirzepatide reduced the apnoea-hypopnoea index by 20-24 events/hour more than placebo (relative reductions of 50-63%), with disease remission in 42-50% of patients and improvements in blood pressure, hypoxic burden and hsCRP [36,37]. Tirzepatide became the first pharmacotherapy approved for OSA, and secondary analyses suggest improvements in OSA-related cardiometabolic risk [37].

Neurodegenerative disease

Observational data linking GLP-1 RA use to lower dementia and Parkinson disease risk generated substantial interest, but randomised evidence is mixed. The phase 3 EVOKE and EVOKE+ trials of oral semaglutide in early symptomatic Alzheimer disease (3,808 participants) were negative for the clinical primary endpoint (change in CDR-SB), although cerebrospinal-fluid biomarkers of tau pathology and neuroinflammation improved [41]. In Parkinson disease, smaller trials of short-acting agents (exenatide, lixisenatide) showed modest motor benefit, but the larger phase 3 Exenatide-PD3 trial was negative [43,44]. A

meta-analysis suggested short-acting agents may be more effective, and that benefits may be more relevant to prevention than to treatment of established disease [42,43]. Overall, GLP-1 RAs are not currently indicated for neurodegenerative disease, and this remains an area of active investigation [42].

Substance use disorders

Emerging evidence suggests GLP-1 signalling modulates mesolimbic reward circuits. A 2026 randomised trial of semaglutide 2.4 mg in patients with alcohol use disorder and obesity reduced alcohol consumption, the first such finding in treatment-seeking individuals [46]. Large observational cohorts report lower risks of alcohol, nicotine, opioid and other substance use disorders among GLP-1 RA users, as well as fewer substance-related hospitalisations and overdoses [47,48]. Notably, DPP-4 inhibitors (which raise endogenous GLP-1) do not reduce alcohol intake, suggesting direct receptor agonism is required [48]. These findings are hypothesis-generating; dedicated trials are ongoing [48].

Anti-inflammatory and other effects

As noted, GLP-1 RAs exert anti-inflammatory effects that are at least partly independent of weight loss and glycaemia, reducing hsCRP and modulating immune pathways [39,40]. These actions likely contribute to the cross-organ benefits observed in cardiovascular, renal and hepatic disease, and may underlie emerging signals in inflammatory and age-related conditions [40].

Body composition: the lean mass caveat

A central concern of particular relevance to health and sport science is that weight loss with GLP-1 RAs comprises both fat and lean (fat-free) mass. Across meta-analyses, lean mass accounts for approximately 25-39% of total weight lost [49,50,51]. Pooled estimates indicate lean body mass reductions of around 0.9 kg versus controls, and up to 5.4 kg with semaglutide 2.4 mg and 5.7 kg with tirzepatide 15 mg in dual-energy X-ray absorptiometry substudies [49,50,53]. Table 3 summarises agent-specific data.

Table 3. Lean mass loss with GLP-1 receptor agonists and tirzepatide.

Agent (trial/analysis)	**Lean mass loss**	**Lean mass as % of total weight loss**	**Reference**

Semaglutide 2.4 mg (STEP 1 substudy)	−5.3 to −6.9 kg	38-45%	[55]
Semaglutide (pooled)	~−5.4 kg	~35%	[49,51]
Tirzepatide 15 mg (SURMOUNT-1 substudy)	−5.67 kg	~26%	[53]
Liraglutide 3.0 mg (>52 weeks)	~−2.6 kg	~27%	[49,51]

Several nuances temper this concern. DXA-measured "lean mass" includes water, organs and the aqueous component of adipose tissue, so true skeletal-muscle loss is smaller than headline figures suggest, estimated at roughly 20% of total weight reduction [55,56]. Moreover, the proportion of lean mass relative to body weight actually increases, because fat loss predominates, and the magnitude of lean mass loss is broadly comparable to that seen with bariatric surgery and caloric restriction [49,51]. Short-term trials generally show preserved handgrip strength and improved self-reported physical function [67,69]. Nonetheless, longitudinal data in older adults raise concern about accelerated sarcopenia and strength loss, particularly with low protein intake and physical inactivity, and weight regain after discontinuation is predominantly fat, which may worsen body composition over cycles of treatment [68,60].

The role of physical activity in preserving skeletal muscle

The interface between pharmacological weight loss and exercise is where this field most directly connects to sport and health science. The pivotal S-LiTE trial randomised 195 adults with obesity, after an initial diet-induced weight loss, to one year of placebo, exercise alone, liraglutide 3.0 mg alone, or exercise plus liraglutide [57]. The combination produced roughly twice the reduction in body-fat percentage of either treatment alone while maintaining lean mass, and exercise alone increased lean mass [57]. A secondary analysis showed that exercise, not liraglutide, drove improvements in physical fitness: combined treatment improved stair-climb time and peak oxygen uptake, and relative muscle strength increased with combined treatment (+3.3%) and liraglutide alone (+1.0%) but fell with placebo (−7.8%)

[58]. A further analysis demonstrated that combined exercise plus liraglutide preserved bone mineral density, whereas liraglutide alone reduced it [59].

Quantitatively, exercise meaningfully changes the composition of weight lost. In a 2026 meta-analysis, lean mass accounted for 29.8% of weight lost with incretin agonists alone and 26.2% with standard lifestyle intervention, but only 17.5% when resistance training was added, and just 12.0% in the S-LiTE combined arm [51]. Another meta-analysis found the fat-free-mass proportion was 7.7% for diet with exercise versus 33.3% for incretin therapies [54]. In older adults, resistance training prevents a large proportion of lean mass loss during dietary weight loss [63]. An emerging pharmacological strategy, the anti-myostatin antibody apitegromab, preserved an additional 1.9 kg of lean mass during tirzepatide therapy in the phase 2 EMBRAZE trial, illustrating active interest in muscle preservation [66].

Major professional bodies now formalise these principles. The joint advisory of the American College of Lifestyle Medicine, American Society for Nutrition, Obesity Medicine Association and The Obesity Society recommends that GLP-1 RAs be prescribed together with structured exercise, including resistance (strength) training plus at least 150 minutes/week of moderate aerobic activity, and emphasises that increased protein intake alone is inadequate without resistance training [56]. The 2026 American Heart Association scientific statement recommends standard physical-activity guidelines (≥150 min/week moderate activity plus muscle-strengthening ≥2 days/week) for patients on GLP-1 RAs while calling for rigorous dose-response trials [63]. The American College of Sports Medicine and related consensus statements likewise endorse resistance training as essential for lean-mass preservation during weight loss [64,65]. Importantly, no large randomised trial has yet tested dedicated progressive resistance training as a primary intervention to prevent muscle loss specifically during semaglutide 2.4 mg or tirzepatide therapy, representing a major evidence gap directly relevant to sport science [67,71].

Summary

GLP-1 receptor agonists have evolved from glucose-lowering and weight-loss agents into genuine multi-organ cardiometabolic therapies. High-quality randomised evidence now demonstrates reductions in major adverse cardiovascular events (SELECT, SUSTAIN-6, SOUL), reduced all-cause mortality (LEADER, SURPASS-CVOT, FLOW), slowed chronic kidney disease progression (FLOW), resolution of steatohepatitis (ESSENCE) and marked improvement in obstructive sleep apnoea (SURMOUNT-OSA) [7,8,9,11,18,32,36]. Signals in

neurodegenerative disease and substance use disorders are intriguing but not yet established, with the negative EVOKE Alzheimer trials underscoring the need for caution [41,46]. A recurring theme is that many benefits are only partly explained by weight loss and glycaemia, pointing to direct anti-inflammatory and tissue-protective mechanisms [40,42].

For the health and sport community, the most actionable insight is that the quality of weight loss matters as much as its quantity. Because roughly a quarter of the weight lost is lean mass, and because physical function and metabolic health depend on skeletal muscle, combining GLP-1 RA therapy with structured physical activity, particularly resistance training, is central to optimising outcomes [49,51,56,57]. Current evidence indicates that exercise can at least halve the proportion of weight lost as lean mass and preserves strength, fitness and bone [51,57,58,59]. Pharmacology and exercise science are therefore complementary rather than competing: the future of obesity and cardiometabolic care lies in their integration. Well-designed randomised trials defining the optimal exercise modality, dose and timing during GLP-1 RA therapy are the key priority for future research [63,71].

Disclosure

Author Contribution

Conceptualization, [S.P.] and [P.M.]; methodology, [W.N.]; software, [D.M.]; validation, [M.S.], [Z.S.] and [P.U.]; formal analysis, [S.P.]; investigation, [P.M.]; resources, [W.N.]; data curation, [D.M.]; writing—original draft preparation, [M.S.]; writing—review and editing, [Z.S.] and [P.U.]; visualization, [S.P.]; supervision, [P.M.]; project administration, [W.N.]; funding acquisition, [D.M.]. All authors have read and agreed to the published version of the manuscript.

Funding Statement

This research received no external funding.

Institutional Review Board Statement

Not applicable. This is a narrative review of previously published literature and did not involve any studies with human participants or animals performed by the authors.

Informed Consent Statement

Not applicable. This study did not involve human participants.

Data Availability Statement

Data sharing is not applicable to this article, as no new data were created or analysed in this review. All data discussed are available in the cited published sources.

Acknowledgments

Not applicable.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Declaration of the Use of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the author(s) used a Google Gemini AI-tool for the purpose of language editing, improving readability, and assisting with the organisation of bibliographic material. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the substantive content of the publication.

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