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Effects of Glucagon-Like Peptide-1 Receptor Agonists (Mono and Combination Therapy) on Energy Expenditure: A Scoping Review

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ABSTRACT

Introduction: Weight loss results in reduced energy expenditure (EE) due to body composition alterations (e.g., fat-free mass and fat mass losses) and mass-independent adaptations in EE (e.g., hormones). Glucagon-like peptide-1 receptor agonists (GLP-1RA) are indicated for obesity management; however, their effects on EE remain unclear.

Methods: In this scoping review, we searched MEDLINE, EMBASE, CINAHL, Web of Science, ProQuest, and Cochrane Library (inception to October 2025) for studies that investigated the effects of GLP-1RA (mono or combination therapy) on EE in humans.

Results: Twenty-three studies were included, 10 assessed GLP-1RA monotherapy (4 exenatide, 4 liraglutide, 1 semaglutide, 1 beinaglutide) and 13 combination therapy (11 dual, 2 triple agonists); drug regimen heterogeneity was high. Most studies assessed resting metabolic rate (RMR); 4 used 24-h whole-room indirect calorimetry; and none applied doubly labeled water. Eight studies (34.8%) concluded that GLP-1RA mono or combination therapy had non-significant effects on EE. Combination with glucagon produced varied impacts on EE components (RQ [$n=3$], RMR [$n=1$], and sleep metabolic rate [n = 1]), whereas combination with glucose-dependent insulinotropic polypeptide (GIP) decreased RQ and increased fat utilization ($n=1$). Eleven studies (47.8%) produced inconclusive results due to the applied statistical analyses.

Conclusion: Acute or chronic GLP-1RA monotherapy does not appear to impact EE independent of weight loss. Combining GLP-1RA with glucagon or GIP may impact EE in different ways, requiring further exploration.

Abbreviations: AEE, activity energy expenditure (the amount of energy burned during physical activity/exercise); AT, adaptive thermogenesis (mass-independent changes in RMR with weight loss); BAT, brown adipose tissue; BIA, bioelectrical impedance analysis; BMR, basal metabolic rate (similar to RMR but assessed in strict conditions, such as after an overnight fast, awakening, and without any movement); DIT, diet-induced thermogenesis (the amount of energy burned to digest, absorb, and metabolize the food after eating); DXA, dual-energy x-ray absorptiometry; EE, energy expenditure (a general term used when not referring to a specific component of EE); FFM, fat-free mass; FM, fat mass; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonists; PRESS, Peer Review of Electronic Search Strategies; PYY, peptide YY; REE, resting energy expenditure (the amount of energy needed to maintain basic physiological functions while at rest; this includes DIT); RMR, resting metabolic rate (the amount of energy needed to maintain basic physiological functions while at rest and after an overnight fast; this does not include DIT); RQ, respiratory quotient (ratio of gas exchanges, indicative of macronutrient oxidation); SMR, sleep energy expenditure (the amount of energy needed to maintain basic physiological functions while sleeping); T3, triiodothyronine; TEE, total energy expenditure (total amount of energy burned in 24 h); WRIC, whole-room indirect calorimetry.

F.T.V. and Z.D. contributed equally to this work.

1 | Introduction

Current weight management strategies include optimizing nutrition and physical activity, as well as additional strategies, including psychological and pharmacological therapy and metabolic and bariatric surgery [1]. Moderate weight loss of 5% over 3–6 months effectively prevents or lowers the risks of several obesity-related conditions [2]. However, adherence and individual responses to interventions vary widely; weight loss and maintenance of the lost weight remain challenging [3–5] and can lead to metabolic adaptations that may favor weight regain.

Weight reduction alters the concentration of several hormones, including glucagon-like peptide-1 (GLP-1), peptide YY (PYY), cholecystokinin, and ghrelin, which influence appetite regulation, and decreases in leptin, triiodothyronine (T3), insulin, and noradrenaline, which are associated with decreases in energy expenditure (EE) [6–8]. A reduction in overall EE of approximately 15.4 ± 8.7 kcal per kg of weight lost is expected [9], with T3, leptin, and sympathetic nervous system activity playing a central role in the hormonal regulation of adaptive thermogenesis (AT) [10]. AT refers to the body's physiological responses to changes in energy balance, including increases in lipolysis, fat oxidation, ketogenesis, gluconeogenesis, glycogen mobilization, and urea genesis, as well as a decrease in the specific metabolic rates of organs and tissues. AT reflects in a reduction in cellular oxygen consumption that is independent of body mass [11, 12], more specifically, fat-free mass (FFM). EE is a key component of energy balance, and the disproportional decline in EE, greater than the expected decrease based on body mass, makes weight loss and maintenance more challenging [13].

Obesity medications, such as GLP-1 receptor agonists (GLP-1RA), have been extensively explored in recent years. GLP-1 slows gastric emptying, increases insulin release, promotes glycogenesis [14], reduces food cravings, and increases satiety [15]. GLP1-RA therapy is effective for weight loss. GLP-1RA monotherapy (e.g., semaglutide and liraglutide) presented approximately 15% body weight reduction after 68 weeks of treatment [16], whereas combination therapy (e.g., tirzepatide [GLP-1RA + glucose-dependent insulinotropic peptide, GIP], retatrutide [GLP-1RA + GIP + glucagon]) shows even more promising results in weight loss of approximately 20% after 72 weeks [17], on par with metabolic and bariatric surgery.

Despite the benefits of GLP-1RA, its impact on EE is unclear, and conflicting findings have been reported [18]. In animal studies, GLP-1RA administration stimulated adipocyte browning and brown adipose tissue (BAT) thermogenesis, ultimately increasing EE [19], whereas GLP-1RA combined with GIP counteracted AT and increased fat oxidation [20]. In 2018, Maciel et al. conducted a systematic review of 24 studies focused on GLP-1RA monotherapy in humans, concluding that GLP-1RA administration may not affect resting metabolic rate (RMR). However, longer-term treatment (i.e., exenatide or liraglutide for 52 weeks) may lead to an increase in RMR [18], although this conclusion was based on only one study that used incorrect statistical analysis (i.e., RMR/FFM ratio) [19]. Included studies have had heterogeneous methodologies and differed in population characteristics (e.g., diabetes vs. no diabetes), drug formulation (e.g., mono vs. combination therapy), dose (e.g., for diabetes vs. obesity management), intervention duration (e.g., acute vs. chronic), analyzed EE components (e.g., RMR vs. total EE [TEE]), EE assessment methods (e.g., whole-room indirect calorimetry [WRIC] vs. indirect calorimetry), and body composition methods (e.g., two- vs. three-component methods) [21–26]. Notably, the impact of body weight and composition changes on EE, as well as the effects of GLP-1RA combination therapy on EE, were not examined; some of these added agents may influence EE in distinct ways. Therefore, we conducted a scoping review to investigate the effects of both GLP-1RA monotherapy and combination therapy on EE in humans. Changes in body weight and composition were also studied, as they are intimately related to EE, and support the investigation of mass-dependent and mass-independent changes in EE, as well as AT and energy balance. We additionally explored direct and indirect hormonal effects on EE. Understanding the effects of these medications on EE may provide essential information on the energy balance of individuals undergoing obesity and diabetes management and support the advancement of precision medicine.

2 | Materials and Methods

This scoping review was performed and reported according to the 2018 Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (Table S1) [27].

2.1 | Study Selection

The PICOS (population, intervention, comparator, outcomes, and studies) strategy was developed following the Peer Review of Electronic Search Strategies (PRESS) guidelines [28], with the following final result.

2.1.1 | Population

Humans of any sex, age, body weight, and health status.

2.1.2 | Intervention

Acute or chronic use of GLP-1 or GLP-1RA alone or in combination with other metabolic hormones (e.g., glucagon, GIP, and PYY). There is a special interest in weight loss–related AT due to the massive and rapid weight loss with these medications. However, we also aimed to explore the effects of GLP-1RAs in acute interventions without weight loss, as this information could help explain their effects on EE during weight loss.

2.1.3 | Comparator

Any controls were accepted, including baseline status, placebo, or other pharmacotherapies.

2.1.4 | Outcomes of Interest

Different terminologies regarding EE and subcomponents have been proposed, which can cause confusion and misinterpretation.

TEE can be simplistically divided into resting EE (REE) and non-REE. In this case, REE would also account for the diet-induced thermogenesis (DIT). Most of the included studies used the term REE; however, they refer only to the measure of RMR (i.e., the amount of energy needed to maintain basic physiological functions while at rest and fasting), not including the DIT. Thus, to avoid possible misinterpretations in this review, we opted to use the terminology RMR instead of REE for consistency, even when the included article used the term REE. Primary outcomes of this review were TEE and subcomponents: RMR, basal metabolic rate (BMR, similar to RMR but assessed in strict conditions, such as after waking up in a WRIC), sleep metabolic rate (SMR), activity EE (AEE), and respiratory quotient (RQ). Considered gold-standard methods for EE assessment were doubly labeled water (objective biomarker and free-living EE assessment) and WRIC (controlled environment). Weight and body composition changes were also studied. Considered gold-standard method for body composition assessment was a multicomponent model that integrates several independent techniques to derive a more accurate estimate, or, alternatively, as a reference method, the dual-energy x-ray absorptiometry (DXA). Body composition terminology was used as in the original paper.

2.1.5 | Study Designs

Controlled experimental trials with quantitative results.

Language was limited to English, Spanish, Portuguese, or Chinese. Case reports, case series, reviews, letters to the editor, book chapters, abstracts, and conference proceedings were excluded. The combination of GLP-1RA with common diabetes medication (e.g., biguanides, sodium-glucose cotransporter 2 inhibitors, and dipeptidyl peptidase-4 inhibitors) was still classified as monotherapy.

2.2 | Information Sources and Search Strategy

MEDLINE, EMBASE, CINAHL, Web of Science, ProQuest, and Cochrane Library were searched from their respective inception dates to June 28, 2023, for relevant studies that investigated the effects of GLP-1RA combination therapy. To update the current understanding of GLP-1RA monotherapy effects [18], we conducted additional searches in the aforementioned databases from 2018 to July 1, 2023. Both searches were later updated on August 12, 2024, and subsequently on October 28, 2025, rerunning in each database to add results from 2023 to 2025. We further scanned the reference list of included studies and related reviews to investigate potential studies for inclusion. The last updated literature full search strategy and syntax is available in Table S2. Keywords can be organized into three conceptual components: (1) GLP-1, GLP-1RA, and related incretin mimetic therapies (e.g., liraglutide, exenatide, and semaglutide); (2) energy metabolism and EE; and (3) combination hormones (e.g., GIP, glucagon, and tirzepatide).

2.3 | Selection of Sources of Evidence

Two experienced reviewers (Z.D. and G.B.) screened titles, abstracts, and full texts using a screening form designed from the eligibility criteria. When uncertainties arose, a third reviewer (F.V.) was consulted, and major disagreements were resolved through discussions between the reviewers or in consultation with the senior author (A.H.).

2.4 | Data Extraction

The team designed and reviewed a data extraction form. Data extracted included study characteristics (e.g., author, year of publication, country, and study design), participant characteristics (e.g., number, sex, age, inclusion criteria, comorbidities, and concomitant medications), intervention and comparator (e.g., medication, dose, regimen, route, and duration of administration), and outcomes (e.g., EE measures; EE measurement method; EE, weight, and body composition at baseline and following intervention). Two reviewers independently extracted data from studies (Z.D., F.V., or G.B.) and then reviewed and standardized the collected data. Disagreements were resolved through discussions between reviewers or in consultation with a third reviewer (F.V. or A.H.).

2.5 | Synthesis Methods

The findings of the included studies were synthesized narratively and supplemented with a descriptive numerical summary. Precision of the EE method (e.g., coefficient of variation) was discussed in only one of the included studies and could not be estimated in most of them due to lack of data. Thus, the studies were categorized based on their reported results as (1) neutral effect on EE: no statistically significant change in absolute EE or in EE after proper adjustments for body weight/composition (see below), when applicable; (2) increased EE; (3) decreased EE; and (4) miscellaneous effect on EE: another effect on EE other than increase or decrease (e.g., changes in RQ or macronutrient rates).

However, some of the included studies were deemed to have an inconclusive effect on EE because they did not account for body weight/composition. We considered adequate body weight/composition adjustments when they were added as part of the statistical model to detect changes in EE [29, 30]. Regression-based analysis (such as ANCOVA and linear modeling), which plots individual data and analyses group effects adjusting for changes in body composition, is considered the most appropriate method to explore EE changes over time, as opposed to mass specific ratio–based analysis (e.g., kcal/kg of body weight or FFM) or simple absolute change analysis (no adjustments for body weight/composition). Adjusting RMR as a ratio to FFM is methodologically incorrect because it assumes proportional scaling, ignores the heterogeneous metabolic activity of FFM tissues, introduces spurious statistical associations, and fails to control for body size [31–33].

To evaluate changes in body composition, mean fat mass (FM) changes of the individual studies were compared to suggested minimal detectable changes of the respective body composition method (i.e., 1 kg of FM for DXA and bioelectrical impedance analysis [BIA]) [30]. AT was estimated by subtracting pre- and post-intervention RMR adjusted for FFM (or available muscle-related data) [13]. To calculate the FFM-adjusted RMR, measured RMR was subtracted from the predicted RMR, estimated using the following equation: $26.7 \times \text{FFM (kg)} + 192.7$ [34]. Although FM is not metabolically inert, its energy requirement is minimal compared to FFM, and thus, FM data were not included in AT calculations in this review. Energy balance of individual studies was estimated by mean changes in FM and FFM (or available muscle-related data) considering (1) 9.3 kcal/g of FM loss and 1.1 kcal/g of FFM or (2) 13.1 kcal/g of FM gain and 2.2 kcal/g of FFM gain [35]. Studies were analyzed separately, considering mass-dependent effects (involving changes in body weight and body composition and AT) or mass-independent effects (AT only) on EE. Although mass-dependent primarily influences RMR, we also included all reported EE components, such as TEE and SMR.

3 | Results

A total of 6449 citations were initially identified in this scoping review through database and citation searches. After removing duplicates, a total of 3423 records underwent title and abstract screening. Of these, 261 studies were assessed in full for eligibility; following a thorough full-text review, 17 eligible articles were included in the final review [36–52]. The updated searches identified an additional 2456 unique citations, among which 49 studies were assessed in full and 6 were deemed eligible for inclusion [20, 53–57]. Figure 1 provides the PRISMA flow diagram outlining, in detail, the screening process.

3.1 | Study Characteristics

Table 1 provides a detailed description of the characteristics of the included studies [20, 36–57]. A total of 844 individuals, balanced in sex (53% females, $n = 444$), participated in the trials. Among included studies with chronic intervention duration, 39% ($n = 9$) were RCTs with parallel designs [20, 36, 37, 39–41, 50, 52, 53], 17% ($n = 4$) performed a single-arm prospective trial [38, 54–56], and only one performed a quasi-experimental trial [57]; but acute interventions were performed by crossover studies ($n = 9$, 39%) [42–49, 51]. Most studies ($n = 20$, 87%) included participants who had overweight or obesity [20, 36, 37, 39, 41–47, 49–57], 43% ($n = 10$) included individuals who had prediabetes or diabetes [37, 40–42, 48, 49, 52–54, 57], and 30% ($n = 7$) included participants who had both overweight/obesity and prediabetes/diabetes [37, 41, 49, 52–54, 57]. Only four studies calculated the sample size based on an EE variable [20, 36, 38, 50]. Most studies (74%, $n = 17$) were published on or after 2018 [20, 36–41, 47–50, 52–57]. All trials included only individuals ≥ 18 years old (no study in pediatrics), and among these, 35% ($n = 8$) also included individuals ≥ 65 years [37, 39, 47–49, 52–54]. Placebo was the most used comparator in included trials (70%, $n = 16$) [20, 36, 37, 39, 41, 43–53].

Studies varied greatly regarding drug regimens (e.g., formulation, dose, and duration) and EE assessment methods. Intervention-wise (Table 1 and Figure 2), most studies investigated either GLP-1RA monotherapy (43%, $n = 10$; published after February 2018) [36–41, 53–56] or dual therapy (48%, $n = 11$) [20, 42–50, 57]. The drugs most frequently tested were synthetic GLP-1 [42–47, 49, 51, 52], exenatide [36, 38, 39, 53], liraglutide [37, 40, 41, 55], and tirzepatide [20, 57]. Hormones used in combination with GLP-1RA included GIP [20, 42, 47–49, 57], glucagon [43, 44, 46, 50], PYY (3–36) [45, 51, 52], and oxyntomodulin [46, 51, 52]. Duration of intervention in the included trials varied from acute (0.75–10.5 h) [42–49, 51] to chronic (14 days to 12 months) [20, 36–41, 50–57].

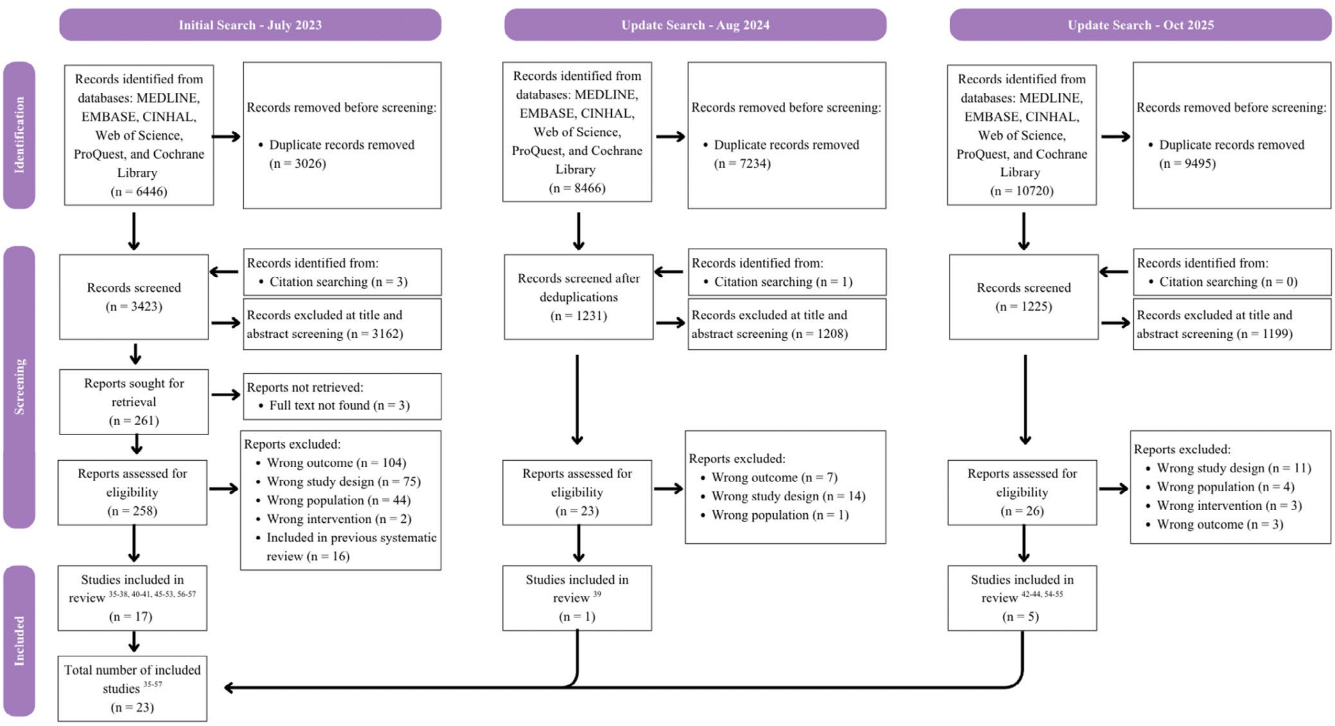

FIGURE 1 | PRISMA flow diagram of included studies in this scoping review investigating the effects of glucagon-like peptide-1 receptor agonists mono and combination therapy on energy expenditure.

TABLE 1 | Characteristics of included studies in this scoping review ($n = 23$) investigating the effects of glucagon-like peptide-1 receptor agonists mono and combination therapy on energy expenditure.

Author, year (country)	Study design	Participant characteristics	Sample size justification	Interventions
Monotherapy: GLP-1RA				
Basolo et al. 2018 [36] (United States)	RCT, double-blind	• *N*: 80 (57.5% female) • Age: Mean 34.4 ± 8.7 years • Comorbidities: Obesity, no diabetes • Medications: Not specified	Based on TEE and ad libitum energy intake ($\alpha = 0.01$, $\beta = 90\%$)	*Intervention* • Drug: Exenatide • Regimen: 10 mcg BID subcut *Comparator* • Placebo Duration: 24 weeks
van Eyk et al. 2020 [37] (Netherlands)	RCT, double-blind	• *N*: 49 (41% female) • Age: Mean 59.9 ± 6.2 years (IG), 59.2 ± 6.8 years (CG) • Comorbidities: Overweight/obesity, T2DM • Medications: Metformin (mandatory), sulfonylurea and insulin (optional)	Not discussed	*Intervention* • Drug: Liraglutide • Regimen: 1.8 mg once daily subcut *Comparator* • Placebo Duration: 26 weeks
Janssen et al. 2020 [38] (Netherlands)	Single-arm prospective trial	• *N*: 24 (0% female) • Age: Mean 34.4 ± 8.7 years • Comorbidities: No diabetes • Medications: None that affects glucose/lipid metabolism	Based on brown adipose tissue activity ($\alpha = 0.05$, $\beta = 80\%$)	*Intervention* • Drug: Exenatide • Regimen: 2 mg once weekly subcut *Comparator* • Baseline status Duration: 12 weeks
Rodgers et al. 2021 [39] (United States)	RCT, single-blind (participant)	• *N*: 67 (100% female) • Age: Mean 43.9 ± 11.9 years (IG), 44.6 ± 13.7 years (CG) • Comorbidities: Overweight/obesity, no diabetes • Medications: Not specified	Based on weight change ($\beta = 83\%$)	*Intervention* • Drug: Exenatide • Regimen: Max 10 mcg daily (2 injections/day) subcut *Comparator* • Placebo + hypocaloric diet Duration: 12 weeks

(Continues)

TABLE 1 | (Continued)

Author, year (country)	Study design	Participant characteristics	Sample size justification	Interventions
Van Ruiten et al. 2022 [53] (Netherlands)	RCT, double-blind	• *N*: 65 (28% female) • Age: Mean 63.5 ± 0.9 years • Comorbidities: Obesity, T2DM • Medications: Metformin (all) +/− sulfonylureas, beta blocker, statin, anti-coagulant, RAS inhibitor, ACE inhibitor, or ARB	Based on blood-oxygen-level-dependent functional magnetic resonance imaging signal changes (β = 85%)	• *Intervention A*: Exenatide + placebo • *Intervention B*: Dapagliflozin + placebo • *Intervention C*: Exenatide + dapagliflozin • *Comparator*: Placebo + placebo *Regimen* • Exenatide: 10 mcg BID subcut • Dapagliflozin: 10 mg once daily PO Duration: 16 weeks
Etoga et al. 2023 [40] (Cameroon)	RCT, single-blind (investigator)	• *N*: 14 (71.4% female) • Age: Median 57 years (IQR 49–61.5) • Comorbidities: Uncontrolled T2DM • Medications: Metformin or metformin + sulfonylureas	Based on insulin sensitivity (α, β not provided)	*Intervention* • Drug: Liraglutide • Regimen: 1.2 mg once daily subcut *Comparator* • Drug: Vildagliptin • Regiment: 50 mg BID PO • Duration: 2 weeks
Silver et al. 2023 [41] (United States)	RCT, double-blind	• *N*: 88 (68% female) • Age: Mean 50.3 ± 10.8 years • Comorbidities: Obesity, prediabetes • Medications: Not specified	Based on weight change (α, β not provided)	*Intervention* • Drug: Liraglutide + placebo (oral) • Regimen: 1.8 mg once daily subcut *Comparator A* • Drug: Sitagliptin + placebo (subcut) • Regimen: 100 mg once daily PO *Comparator B* • Hypocaloric diet Duration: 16 weeks
Alissou et al. 2025 [54] (France)	Single-arm prospective trial	• *N*: 106 (68.9% female) • Age: Mean 52.2 ± 12.1 years • Comorbidities: Obesity, T2DM (35.8%), bariatric surgery (21.7%) • Medications: 5.7% were previously exposed to GLP-1RA	Not calculated	*Intervention* • Drug: Semaglutide • Regimen: 2.4 mg once weekly subcut *Comparator* • Baseline status Duration: 12 months

(Continues)

TABLE 1 | (Continued)

Author, year (country)	Study design	Participant characteristics	Sample size justification	Interventions
Basolo et al. 2025 [55] (Italy)	Single-arm prospective trial	• N: 11 (72.7% female) • Age: Mean 49 ± 9 years • Comorbidities: Obesity, no diabetes • Medications: Not specified	Not discussed	*Intervention* • Drug: Liraglutide • Regimen: 3.0 mg once daily subcut *Comparator* • Baseline status Duration: 6 months
Liu et al. 2025 [56] (China)	Single-arm prospective trial	• *N*: 33 (75.8% female) • Age: 35.33 ± 8.0 years • Comorbidities: Obesity, no diabetes • Medications: Not specified	Not discussed	*Intervention* • Drug: Beinaglutide + lifestyle intervention (hypocaloric diet plus exercise) • Regimen: 0.1 mg thrice daily subcut, 5 min before each major meal *Comparator* • Baseline status Duration: 12 weeks
Dual therapy: GLP-1RA in combination with another drug				
Daousi et al. 2009 [42] (England)	Randomized crossover trial, double-blind	• *N*: 12 (0% female) • Age: Mean 51 years (range 37–62)—obesity + T2DM; 39 years (range 27–49) healthy controls • Comorbidities: Overweight/obesity and T2DM • Medications: Not specified	Not discussed	• *Intervention A*: Synthetic human GLP-1 • *Intervention B*: Synthetic human GIP • *Intervention C*: Synthetic human GLP-1 + GIP • *Comparator*: Dextrose *Regimen* • GLP-1: 1 pmol/kg/min IV • GIP: 2 pmol/kg/min IV Duration: 4 h
Tan et al. 2013 [43] (United Kingdom)	Randomized crossover trial, double-blind	• *N*: 10 (70% female) • Age: 25.8 years (range 23–49) • Comorbidities: Overweight/obesity and no diabetes • Medications: Not specified	Not discussed	• *Intervention A*: Synthetic human GLP-1 • *Intervention B*: Glucagon • *Intervention C*: Synthetic human GLP-1 + glucagon • *Comparator*: Placebo *Regimen* • GLP-1: 0.8 pmol/kg/min IV • Glucagon: 50 ng/kg/min IV • Duration: 0.75 h

(Continues)

TABLE 1 | (Continued)

Author, year (country)	Study design	Participant characteristics	Sample size justification	Interventions
Cegla et al. 2014 [44] (United Kingdom)	Randomized crossover trial, double-blind	• *N*: 13 (31% female) • Age: Mean 31.6 years (range 21–41) • Comorbidities: Overweight/obesity, no diabetes • Medications: Not specified	Not discussed	• *Intervention A*: GLP-1 • *Intervention B*: Glucagon • *Intervention C*: GLP-1 + Glucagon • *Comparator*: Placebo *Regimen* • *GLP-1*: 0.4 pmol/kg/min IV • *Glucagon*: 2.8 pmol/kg/min IV Duration: 2 h
Schmidt et al. 2014 [45] (Denmark)	Randomized crossover trial, double-blind	• *N*: 25 (0% female) • Age: Mean 33.0 ± 9.0 years • Comorbidities: Overweight, no diabetes • Medications: Not specified	Based on ad libitum energy intake ($\alpha = 0.05$, $\beta = 80\%$)	• *Intervention A*: Synthetic human GLP-1 • *Intervention B*: Synthetic human PYY • *Intervention C*: Synthetic human GLP-1 + PYY • *Comparator*: Placebo *Regimen* • GLP1: 1 pmol/kg/min IV • PYY: 0.8 pmol/kg/min IV Duration: 2.5 h
Bagger et al. 2015 [46] (Denmark)	Randomized crossover trial, double-blind	• *N*: 15 (0% female) • Age: Mean 22 years (range 18–32) • Comorbidities: Overweight/normal weight, no diabetes • Medications: None	Not discussed	• *Intervention A*: GLP-1 • *Intervention B*: Glucagon • *Intervention C*: Oxyntomodulin • *Intervention D*: GLP-1 + glucagon • *Comparator*: Placebo *Regimen* • *GLP-1*: 1 pmol/kg/min IV • *Glucagon*: 0.86 pmol/kg/min IV • *Oxyntomodulin*: 3 pmol/kg/min IV • Duration: 4 h
Bergmann et al. 2019 [47] (Denmark)	Randomized crossover trial, double-blind	• *N*: 17 (0% female) • Age: Median 34 years (IQR 29–51) • Comorbidities: Overweight/obesity, no diabetes • Medications: Not specified	Based on ad libitum energy intake ($\alpha = 0.05$, $\beta = 80\%$)	• *Intervention A*: Isoglycemic glucose + GLP-1 • *Intervention B*: Isoglycemic glucose + synthetic human GIP • *Intervention C*: Isoglycemic glucose + GLP-1 + GIP • *Comparator*: Isoglycemic glucose + placebo *Regimen* • GLP-1: 1 pmol/kg/min IV • GIP: 4 pmol/kg/min IV Duration: 3.5–3.75 h

(Continues)

TABLE 1 | (Continued)

Author, year (country)	Study design	Participant characteristics	Sample size justification	Interventions
Bergmann et al. 2020 [48] (Denmark)	Randomized crossover trial, double-blind	• *N*: 22 (0% female) • Age: Mean 61.0 ± 2 years • Comorbidities: T2DM • Medications: metformin and background GLP-1RA for at least 3 months	Based on ad libitum energy intake ($\alpha = 0.05$, $\beta = 80\%$)	*Intervention* • Drug: Synthetic human GIP • Regimen: 4 pmol/kg/min IV • Background GLP-1RA (liraglutide [$n = 21$] or dulaglutide [$n = 1$]) *Comparator* • Placebo Duration: 5 h
Stensen et al. 2022 [49] (Denmark)	Randomized crossover trial, double-blind	• *N*: 10 (0% female) • Age: 63.3 years (range 44–72) • Comorbidities: Overweight/obesity and T2DM • Medications: metformin (90% of participants)	Not discussed	• *Intervention*: Synthetic human GLP-1 + GIPR antagonist GIP (3–30) • *Comparator*: Synthetic human GLP-1 + placebo *Regimen* • GLP-1: 0.75 pmol/kg/min IV • GIPR antagonist: 1200 pmol/kg/min IV Duration: 3 h
Corbin et al. 2023 [50] (United States)	RCT, double-blind	• *N*: 35 (32.1% female) • Age: Mean 36.0 ± 7.7 years • Comorbidities: Overweight/obesity, no diabetes • Medications: Not specified	Based on SEE ($\alpha = 0.05$, $\beta = 88.5\%$)	*Intervention* • Drug: GLP-1 + glucagon receptor agonist (SAR425899) + hypocaloric diet • Regimen: 0.2 mg/day subcut *Comparator* • Placebo + hypocaloric diet Duration: 19 days
Ravussin et al. 2025 [20] (United States)	RCT, double-blind	• *N*: 55 (83.6% female) • Age: 45.5 ± 9.8 years (IG), 48.1 ± 10.7 years (CG) • Comorbidities: Obesity, no T2DM • Medications: Not specified	Based on difference of 100 ± 117 kcal/day in sleeping metabolic rate ($\alpha = 0.05$, $\beta = 80\%$)	*Intervention* • Drug: Tirzepatide + dietary intervention • Regimen: 15 mg once weekly subcut *Comparator*: • Placebo + dietary intervention Duration: 18 weeks

(Continues)

TABLE 1 | (Continued)

Author, year (country)	Study design	Participant characteristics	Sample size justification	Interventions
Schiavo et al. 2025 [57] (Italy)	Quasi-experimental trial	• *N*: 60 (55% female) • Age: ≥ 18 years • Comorbidities: Obesity or overweight with at least one weight-related comorbidity (e.g., T2DM) • Medications: Not specified	Not discussed	*Intervention* • Drug: Tirzepatide + hypocaloric diet • Regimen: 5.0 mg once weekly subcut *Comparator* • Tirzepatide + low-energy ketogenic therapy Duration: 12 weeks
Triple therapy: GLP-1RA in combination with two other drugs				
Tan et al. 2017 [51] (United Kingdom)	Randomized crossover trial, single-blind (participant)	• *N*: 7 (71% female) • Age: Mean 45.0 ± 11 years • Comorbidities: Obesity and no diabetes • Medications: Not specified	Based on ad libitum intake ($\alpha = 0.05$, $\beta = 80\%$)	• *Intervention*: Synthetic human GLP-1 + PYY + oxyntomodulin • *Comparator*: Placebo *Regimen* • GLP-1: 4 pmol/kg/min subcut • PYY: 0.4 pmol/kg/min subcut • Oxyntomodulin: 4 pmol/kg/min subcut Duration: 10.5 h
Behary et al. 2019 [52] (England)	RCT, single-blind (participant)	• *N*: 26 (42% female) • Age: Mean 55.9 ± 8.5 years (IG), 53.5 ± 8.5 years (CG) • Comorbidities: Obesity and prediabetes/diabetes • Medications: Metformin (45%–47% of participants)	Based on weight change ($\alpha = 0.05$, $\beta = 85\%$)	• *Intervention*: Synthetic human GLP-1 + PYY + oxyntomodulin • *Comparator*: Placebo *Regimen* • GLP-1: 4 pmol/kg/min subcut for 12 h/day • PYY: 0.4 pmol/kg/min subcut for 12 h/day • Oxyntomodulin: 4 pmol/kg/min subcut for 12 h/day Duration: 4 weeks

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; BID, twice daily; CG, comparator group; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; IG, intervention group; IQR, interquartile range; IV, intravenously; PO, by mouth; PYY, peptide YY; RAS, renin–angiotensin system; RCT, randomized controlled trial; Subcut, subcutaneously; T2DM, Type 2 diabetes mellitus.

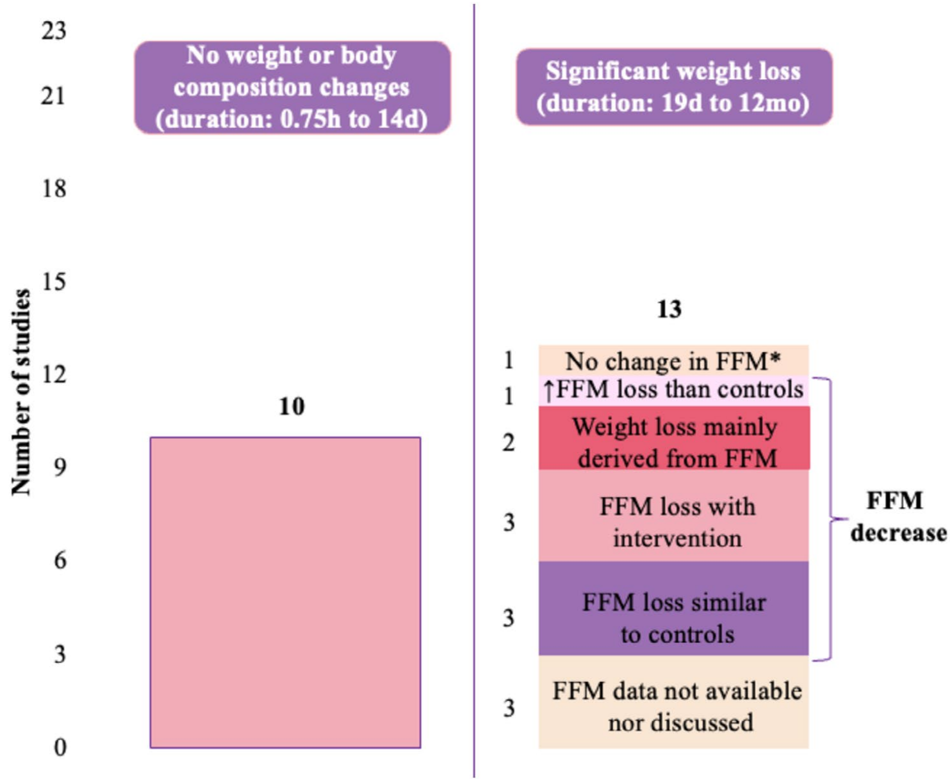

FIGURE 2 | Weight loss and fat-free mass changes after glucagon-like peptide-1 receptor agonists mono and combination therapy of studies included in this scoping review ($n = 23$). *Weight loss at Week 5 but no significant changes at Week 24.

3.2 | Weight and Body Composition Variance and Energy Balance

The impact of the interventions on body weight and composition is fully described in Table 2. All chronic interventions promoted negative energy balance (from −4820 to −116,127 kcal) and reported that individuals lost weight [20, 36–39, 41, 50, 52–57], except for one study with the shortest intervention duration (i.e., 2 weeks) using a low liraglutide dose (i.e., 1.2 mg/day) [40]. Of note, Basolo et al. [36] found a greater weight reduction in the first 5 weeks compared to placebo but not at the end of the 24-week intervention; they also did not report differences in body composition. Body composition was evaluated in all chronic interventions using DXA [20, 36, 41, 50, 54, 55], bioimpedance spectroscopy [53], or BIA [37–40, 52, 56, 57], in addition to two acute interventions [42, 45, 54] also using BIA. However, Liu et al. [56] did not provide muscle-related data, and this could not be estimated. The terminology of the reported muscle-related variables varied and included FFM, lean soft tissue, lean mass, lean body mass, and muscle mass. Weight loss and FFM changes are summarized in Figure 3. Most studies identified body composition changes above the minimal detectable change, except for Janssen et al. [38] who reported significant weight and FFM loss but no changes in FM (Δ ~ 0.4 kg).

3.3 | Energy Expenditure

In terms of EE assessment (Figure 2), indirect calorimetry was used in all studies (no studies with doubly labeled water), and four (17%) used WRIC for TEE assessment [20, 36, 50, 55]. RMR was the most reported EE component (87%, $n = 20$) [20, 37–45, 47–54, 56, 57], and some studies also reported RQ (67%, $n = 14$) [20, 37, 38, 41–45, 47–53, 55]. Additional parameters assessed included DIT [36, 39, 46, 50, 52, 55], SMR [20, 36, 50, 55], AEE [36, 52], macronutrient rates [20, 55], BMR [50], and estimation of an inactive, awake, and fed state [55]. Tables 3 and 4 describe the EE assessment method and analyzed components and specific methods, estimations of AT and energy balance (when possible), and the included studies' findings concerning mass-dependent or mass-independent effects on EE, respectively. Of the included studies, only Basolo et al. [55] have assessed AT, subtracting the measured TEE by a predicted TEE obtained by linear regression analysis and confirmed by a linear mixed-effects model with adjustments. The authors concluded that there was no evidence of AT, termed as metabolic adaptation, even though AT should be estimated from changes in RMR rather than TEE. We were able to estimate AT for five studies; of note, no statistical analysis was performed, and these calculations were based on the average or median of RMR and muscle-related data. Two studies presented a measured RMR greater than the predicted at baseline, with a subsequent decrease in the range of this difference after the intervention, but still presenting a greater measured RMR than the predicted [20, 41]. Two studies presented a predicted RMR greater than the measured at baseline, and this difference was even worse post-intervention [39, 57]. Finally, one study started with a measured RMR greater than the predicted; however, after the intervention, the predicted was greater than the measured [52]. We could not estimate AT for seven studies due to lack of data. General effects on EE are summarized in Figure 2 and discussed below.

TABLE 2 | Summary of the effects of glucagon-like peptide-1 receptor agonists isolated or in combination with other drugs on body weight and composition included in this scoping review ($n = 23$).

Author, year (country)	Interventions	BC technique	Baseline weight/BC	After intervention/ comparator weight/BC	Conclusion
Monotherapy: GLP-1RA					
Basolo et al. 2018 [36] (United States)	Exenatide vs. placebo	DXA	**Weight** Exenatide: 105.5 ± 19.2 kg Placebo: 108.8 ± 20.7 kg **BC** Exenatide FFM (kg): 34.6 ± 11.5 Placebo FFM (kg): 37.9 ± 8.7 Exenatide FM (kg):27.9 ± 8.8 Placebo FM (kg): 30.8 ± 8.7 Exenatide FM (%): 44.0 ± 6.9 Placebo FM (%): 44.4 ± 8.7	**Weight** Absolute data presented in graphs Exenatide: −0.039 kg/week at 5 weeks (weight trajectory difference from placebo) Weight change (24 weeks): −1.72 kg (95% CI −5.77, 2.30) **BC** BC data not provided but reported no difference	Exenatide presented a greater weight loss rate over the 5 initial weeks compared to placebo ($p = 0.02$) No significant differences in body weight ($p = 0.39$) or BC (data not shown) in exenatide vs. placebo at 24 weeks MDC: BC data not provided
van Eyk et al. 2020 [37] (Netherlands)	Liraglutide vs. placebo	BIA	**Weight** Liraglutide: 98.4 ± 13.8 kg Placebo: 94.5 ± 13.1 kg **BC** Liraglutide LBM (kg): 62.2 ± 9.4 Placebo LBM (kg): 60.0 ± 12.1 Liraglutide LBM (%): 63.9 ± 10.2 Placebo LBM (%): 63.4 ± 8.8 Liraglutide FM* (kg): 36.2 Placebo FM* (kg): 34.5 *Calculated from LBM (kg)	Change (baseline vs. Week 26) **Weight** Liraglutide: −4.3 ± 3.8 kg Placebo: 0.1 ± 2.5 kg Liraglutide vs. placebo: −4.5 kg (95% CI −6.4, −2.6) **BC** Liraglutide LBM (kg): −2.1 ± 2.9 Placebo LBM (kg): −0.2 ± 1.6 Liraglutide vs. placebo LBM (kg): −1.7 kg (95% CI −3.1, −0.4) Liraglutide LBM (%): 0.5 ± 3.0 Placebo LBM (%): −0.2 ± 2.2 Liraglutide vs. placebo LBM (%): 0.7 kg (95% CI −0.8, 2.2) Liraglutide FM* (kg): 34.0 (−2.2) Placebo FM* (kg): 34.8 (+0.3) *Calculated from LBM (kg)	Liraglutide decreased body weight ($p < 0.001$) and LBM ($p = 0.012$) compared to placebo at Week 26 ΔFM ~ 2.2 kg* = above MDC *Calculated from LBM

(Continues)

TABLE 2 | (Continued)

Author, year (country)	Interventions	BC technique	Baseline weight/BC	After intervention/comparator weight/BC	Conclusion
Janssen et al. 2020 [38] (Netherlands)	Exenatide	BIA	**Weight** 80.4 ± 2.1 kg **BC** LM (kg): 66.8 ± 1.6 FM (kg): 13.6 ± 0.9 FM (%): 16.7 ± 0.9	**Weight** 78.9 ± 2.1 kg Change (baseline vs. Week 12): −1.5 ± 0.4 kg **BC** LM (kg): 65.8 ± 1.6 FM (kg): 13.2 ± 0.8 FM (%): 16.5 ± 0.8	Exenatide decreased body weight and LM in the overall cohort ($p < 0.01$) at Week 12, with no changes in FM (pre–post study) ΔFM ~ 0.4 kg = below MDC
Rodgers et al. 2021 [39] (United States)	Exenatide vs. placebo + hypocaloric diet	BIA	**Weight** Exenatide: 93.9 ± 14.9 kg Diet: 94.7 ± 13.6 kg **BC** Exenatide FM (%): 43.7 ± 4.1 Diet FM (%): 43.8 ± 3.8 Exenatide FFM* (kg): 52.9 Diet FFM* (kg): 53.2 *Calculated from FM%	**Weight** Exenatide: 87.7 ± 13.7 kg Diet: 87.5 ± 11.9 kg **BC** Exenatide FM (%): 43.3 ± 4.3 Diet FM (%): 42.0 ± 4.6 Exenatide FFM* (kg): 49.7 Diet FFM* (kg): 50.8 *Calculated from FM%	Both groups had significant and similar reductions in body weight ($p < 0.001$), but only diet decreased FM ($p = 0.02$) at Week 12 ΔFM ~ 3.1 kg (calculated from %FM mean) = above MDC

(Continues)

TABLE 2 | (Continued)

Author, year (country)	Interventions	BC technique	Baseline weight/BC	After intervention/comparator weight/BC	Conclusion
Van Ruiten et al. 2022 [53] (Netherlands)	Exenatide vs. dapagliflozin vs. exenatide + dapagliflozin vs. placebo	Bioimpedance spectroscopy	**Weight** Exenatide: 96.6 ± 13.3 kg Dapagliflozin: 97.8 ± 15.4 kg Exenatide + dapagliflozin: 93.6 ± 13.4 kg Placebo: 99.1 ± 21.9 kg **BC** Exenatide FM (%): 38.6 ± 8.6 Dapagliflozin FM (%): 34.9 ± 5.5 Exenatide + dapagliflozin FM (%): 34.9 ± 6.2 Placebo FM (%): 34.9 ± 7.4 Exenatide FFM* (kg): 59.3 Dapagliflozin FFM* (kg): 63.7 Exenatide + dapagliflozin FFM* (kg): 60.9 Placebo FFM* (kg): 64.5 *Calculated from FM%	Change (baseline vs. Week 16) **Weight** Exenatide: −1.4 ± 0.5 kg Dapagliflozin: −2.5 ± 0.6 kg Exenatide + dapagliflozin: −2.8 ± 0.5 kg **BC** Exenatide FM (%): −2.2 ± 1.1 kg Dapagliflozin FM (%): −1.9 ± 1.1 kg Exenatide + Dapagliflozin FM (%): −3.0 ± 1.1 kg Exenatide FFM* (kg): 60.5 (+1.2) Dapagliflozin FFM* (kg): 63.9 (+0.2) Exenatide + dapagliflozin FFM* (kg): 61.8 (+0.9) *Calculated from FM%	Exenatide ($p < 0.01$), dapagliflozin ($p < 0.001$), and exenatide + dapagliflozin ($p < 0.001$) all reduced body weight compared to placebo at 16 weeks Exenatide ($p < 0.05$), and exenatide + dapagliflozin ($p < 0.01$) reduced FM% at Week 16 ΔFM ~ 2.6 kg (calculated from %FM mean) = above MDC

(Continues)

TABLE 2 | (Continued)

Author, year (country)	Interventions	BC technique	Baseline weight/BC	After intervention/ comparator weight/BC	Conclusion
Etoga et al. 2023 [40] (Cameroon)	Liraglutide vs. vildagliptin	BIA	**Weight** Liraglutide: Median 91.7 kg (IQR 81.6, 100) Vildagliptin: Median 77.5 kg (IQR 66.1, 92.4) **BC** Liraglutide LM (kg): Median 59.6 (IQR 53.4, 66.7) Vildagliptin LM (kg): Median 48.3 (IQR 41.0, 53.3) Liraglutide FM (kg): Median 25.7 (IQR 24.3, 38.2) Vildagliptin FM (kg): Median 29.9 (IQR 17.4, 44.0) Liraglutide FM (%): Median 33.3 (IQR 29.5, 41.7) Vildagliptin FM (%): Median 36.9 (IQR 26.4, 47.6)	**Weight** Liraglutide: Median 91.1 kg (IQR 79.8, 97.1) Vildagliptin: Median 78.6 kg (IQR 58.7, 92.0) **BC** Liraglutide LM (kg): Median 58.6 (IQR 52.3, 69.8) Vildagliptin LM (kg): Median 48.1 (IQR 42.2, 54.0) Liraglutide FM (kg): Median 25.1 (IQR 23.2, 38.7) Vildagliptin FM (kg): Median 25.9 (IQR 16.5, 43.8) Liraglutide FM (%): Median 30.0 (IQR 26.6, 42.3) Vildagliptin FM (%): median 37.3 (IQR 26.5, 47.7)	No changes in body weight, LM, or FM at Week 2 for both groups ΔFM ~ 0.6 kg (median) = bellow MDC

(Continues)

TABLE 2 | (Continued)

Author, year (country)	Interventions	BC technique	Baseline weight/BC	After intervention/comparator weight/BC	Conclusion
Silver et al. 2023 [41] (United States)	Liraglutide + placebo vs. sitagliptin + placebo vs. hypocaloric diet	DXA	**Weight** Liraglutide: 108.5 ± 21.6 kg Sitagliptin: 112.4 ± 22.8 kg Diet: 109.9 ± 16.9 kg **BC** Liraglutide LM (kg): 53.6 ± 9.3 Sitagliptin LM (kg): 57.5 ± 13.9 Diet LM (kg): 56.0 ± 9.7 Liraglutide FM (kg): 49.4 ± 12.7 Sitagliptin FM (kg): 49.8 ± 14.2 Diet FM (kg): 49.5 ± 14.4 Liraglutide FM (%): 47.1 ± 5.8 Sitagliptin FM (%): 45.8 ± 7.5 Diet FM (%): 46.8 ± 6.7	**Weight** Liraglutide: 106.3 ± 22.5 kg Sitagliptin: 112.1 ± 23.4 kg Diet: 105.2 ± 18.2 kg **BC** Liraglutide LM (kg): 52.8 ± 9.8 Sitagliptin LM (kg): 56.9 ± 13.7 Diet LM (kg): 56.7 ± 9.6 Liraglutide FM (kg): 47.1 ± 13.6 Sitagliptin FM (kg): 51.5 ± 13.2 Diet FM (kg): 47.2 ± 14.6 Liraglutide FM (%): 47.1 ± 5.7 Sitagliptin FM (%): 47.6 ± 4.6 Diet FM (%): 45.2 ± 7.8	Liraglutide and diet decreased weight and FM, with diet presenting a higher decrease for both at Week 16 Liraglutide decreased LM ($p = 0.007$), although it was not significantly different from the other two groups at Week 16 ΔFM ~ 2.3 kg = above MDC
Alissou et al. 2025 [54] (France)	Semaglutide	DXA BIA (total water)	**Weight** 127.2 ± 23.3 kg **BC** LM (kg): 58.2 ± 12.1 FM (kg): 65.5 ± 13.6 FM (%): 51.8 ± 4.8	Change (baseline vs. Month 12) **Weight** Absolute data presented in graphs −15.6 ± 10.6 kg **BC** LM (kg): −3.27 ± 3.30 FM (kg): −12.1 ± 8.0 FM (%): −18.9 ± 12.3	At month 12, semaglutide reduced weight and FM, and increased %LM ($p < 0.0001$) At Month 7, reduction in LM ($p < 0.0001$), and it stabilized until Month 12. Similar findings for appendicular skeletal muscle mass and total water ΔFM ~ 12.1 kg = above MDC

(Continues)

TABLE 2 | (Continued)

Author, year (country)	Interventions	BC technique	Baseline weight/BC	After intervention/ comparator weight/BC	Conclusion
Basolo et al. 2025 [55] (Italy)	Liraglutide	DXA	**Weight** 103.3 ± 18.1 kg **BC** LST (kg): 53.3 ± 12.9 FM (kg): 47.0 ± 8.6	**Weight** 92.8 ± 17.1 kg **BC** LST (kg): 51.6 ± 12.9 FM (kg): 38.3 ± 8.8	At Month 6, liraglutide decreased weight ($p < 0.05$), mainly driven by FM (85%), with a minor reduction in LST ($p < 0.05$) ΔFM ~ 8.7 kg = above MDC
Liu et al. 2025 [56] (China)	Beinaglutide	BIA	**BMI** Median 31.1 kg/m^2 (IQR 30.3, 33.3) **BC** FM (kg): 33.9 ± 6.2 FM (%): 38.7 ± 5.8	**BMI** Week 4: Median 29.0 kg/m^2 (IQR 28.2, 30.6) Week 12: Median 27.5 kg/m^2 (IQR 26.4, 28.9) **BC** Week 4: FM (kg): 28.4 ± 5.2 FM (%): 35.4 ± 5.6 Week 12: FM (kg): 24.2 ± 5.3 FM (%): 31.3 ± 6.1	At Month 12, beinaglutide decreased BMI and FM% ($p < 0.001$) ΔFM ~ 9.7 kg = above MDC
Dual therapy: GLP-1RA and another drug					
Daousi et al. 2009 [42] (England)	GLP-1 vs. GIP vs. GLP-1 + GIP vs. dextrose	BIA	**Weight** Obesity + T2DM: 126.9 ± 11.4 kg Healthy: 82.5 ± 3.2 kg **BC** Obesity + T2DM FM (%): 38.6 ± 2.6 Healthy FM (%): 19.7 ± 0.9	Not applicable	Not applicable
Tan et al. 2013 [43] (United Kingdom)	GLP-1 vs. Glucagon alone vs. GLP-1 + glucagon vs. placebo	Data not evaluated	**Weight** 91.3 kg (range 77.2–101.5 kg)	Not applicable	Not applicable
Cegla et al. 2014 [44] (United Kingdom)	GLP-1 vs. glucagon vs. GLP-1 + glucagon vs. placebo	Data not evaluated	**Weight** Mean BMI 27 kg/m^2 (range 24–32.9)	Not applicable	Not applicable

(Continues)

TABLE 2 | (Continued)

Author, year (country)	Interventions	BC technique	Baseline weight/BC	After intervention/ comparator weight/BC	Conclusion
Schmidt et al. 2014 [45] (Denmark)	GLP-1 vs. PYY vs. GLP-1 + PYY vs. placebo	BIA	**BMI** BMI ± 29.03.0 kg/m^2 **BC** FM (%) 28.0 ± 4.0	Data not provided but reported no difference	No differences in weight or BC
Bagger et al. 2015 [46] (Denmark)	GLP-1 vs. glucagon vs. oxyntomodulin vs. GLP-1 + glucagon vs. placebo	Data not evaluated	Data not evaluated	Not applicable	Not applicable
Bergmann et al. 2019 [47] (Denmark)	IIGI + GLP-1 vs. IIGI + GIP vs. IIGI + GLP-1 + GIP vs. IIGI + placebo	Data not evaluated	**Weight** Median 100 kg (IQR 88–115)	Not applicable	Not applicable
Bergmann et al. 2020 [48] (Denmark)	Background GLP-1RA + GIP vs. placebo	Data not evaluated	**Weight** 103.5 ± 3.0 kg	Not applicable	Not applicable
Stensen et al. 2022 [49] (Denmark)	GLP-1 + GIPR antagonist GIP (3–30) vs. GLP-1 + placebo	Data not evaluated	**Weight** 100.9 kg (range 88.9–113.3)	Not applicable	Not applicable
Corbin et al. 2023 [50] (United States)	GLP-1 + glucagon receptor agonist + hypocaloric diet vs. placebo + hypocaloric diet	DXA	**Weight** GLP-1 + glucagon: 93.76 ± 10.10 kg Placebo: 91.54 ± 12.15 kg **BC** GLP-1 + glucagon FFM (kg): 58.3 ± 9.3 Placebo FFM (kg): 57.9 ± 11.6 GLP-1 + glucagon FM (kg): 35.4 ± 6.7 Placebo FM (kg): 33.6 ± 6.1	Change (baseline vs. Day 20) **Weight** GLP-1 + glucagon: −4.83 ± 1.44 kg Placebo: −3.68 ± 1.37 kg **BC** GLP-1 + glucagon FFM (kg): −2.4 ± 1.2 Placebo FFM (kg): −1.8 ± 0.8 GLP-1 + glucagon FM (kg): −1.5 ± 0.5 Placebo FM (kg): −1.0 ± 0.5	Both groups decreased body weight, FM, and FFM at Day 20 ($p < 0.0001$) GLP-1 + glucagon presented a greater decrease in body weight ($p = 0.002$) and FM ($p = 0.01$) than placebo, with no differences for FFM ΔFM ~ 1.5 kg = above MDC

(Continues)

TABLE 2 | (Continued)

Author, year (country)	Interventions	BC technique	Baseline weight/BC	After intervention/ comparator weight/BC	Conclusion
Ravussin et al. 2025 [20] (United States)	Tirzepatide	DXA	**Weight** Tirzepatide: 102.5 ± 15.1 kg Placebo: 103.1 ± 12.6 kg **BC** Tirzepatide: FFM (kg): 54.9 ± 9.9 FM (kg): 47.2 ± 8.9 Placebo: FFM (kg): 54.6 ± 12.0 FM (kg): 48.1 ± 8.3	**Weight** Tirzepatide: 85.0 ± 13.2 kg Placebo: 93.7 ± 11.2 kg **BC** Tirzepatide: FFM (kg):49.0 ± 9.4 FM (kg): 35.5 ± 7.3 Placebo: FFM (kg): 52.2 ± 11.5 FM (kg): 41.1 ± 8.6	At Week 18, both groups decreased weight, FM, and FFM, with a greater reduction with tirzepatide ($p < 0.0001$) ΔFM: ~11.7 kg = above MDC
Schiavo et al. 2025 [57] (Italy)	Tirzepatide + LCD vs. tirzepatide + LEKT	BIA	**Weight** LCD: 124.3 ± 23.8 kg LEKT: 121.9 ± 23.6 kg **BC** LCD: FFM (kg): 60.6 ± 12.8 FM (kg): 58.4 ± 13.0 LEKT: FFM (kg): 59.9 ± 14.3 FM (kg): 56.4 ± 11.6	Change (baseline vs. Week 12) **Weight** LCD: −9.8% ± 2.9% LEKT: −10.2% ± 2.5% **BC** LCD: FFM (kg): −4.29% ± 1.31% (58.0 kg*) FM (kg): −10.2% ± 3.1% (52.4 kg*) LEKT: FFM (kg): −0.50% ± 0.82% (59.6 kg*) FM (kg): −13.4% ± 2.8% (48.8 kg*) *Calculated from baseline	At Week 12, both groups decreased weight, with no difference in weight loss between groups ($p = 0.665$). Both groups decreased FM and FFM, but tirzepatide + LEKT had a greater FM decrease ($p = 0.042$) and a smaller FFM decrease ($p = 0.039$) ΔFM LCD: ~ 6 kg = above MDC ΔFM LEKT: ~7.6 kg = above MDC
Triple therapy: GLP-1RA in combination with two other drugs					
Tan et al. 2017 [51] (United Kingdom)	GLP-1 + oxyntomodulin + PYY vs. placebo	Data not evaluated	**Weight** 104.8 ± 22.9 kg	Not applicable	Not applicable

(Continues)

TABLE 2 | (Continued)

Author, year (country)	Interventions	BC technique	Baseline weight/BC	After intervention/ comparator weight/BC	Conclusion
Behary et al. 2019 [52] (England)	GLP-1 + oxyntomodulin + PYY vs. placebo	BIA	**Weight** Intervention: 112.6 ± 26.7 kg Placebo: 119.2 ± 25.1 kg **BC** Intervention MM (kg): 63.3 Placebo MM (kg): 67.3 Intervention FM (kg): 43.4 Placebo FM (kg): 48.3	Absolute and change (baseline vs. Week 4) **Weight** Intervention: 108.2 kg (−4.4 [95% CI −5.4, −3.5]) Placebo: 116.8 kg (−2.5 [95% CI 4.1, −0.9]) Intervention vs. placebo: Δ1.9 (95% CI 0.3, 3.5) **BC** Intervention MM (kg): 61.6 (−1.7 [95% CI −2.8, −0.7]) Placebo MM (kg): 66.4 (−0.9 [95% CI −1.7, −0.2]) Intervention vs. placebo MM: Δ0.8 (95% CI −0.5, 2.1) Intervention FM (kg): 40.9 (−2.4 [95% CI −3.2, −1.7]) Placebo FM (kg): 47.0 (−1.3 [95% CI −2.9, 0.3]) Intervention vs. placebo FM: Δ1.1 (95% CI −0.4, 2.7)	Both groups decreased body weight, and MM, but only intervention decreased FM at Week 4 Intervention presented a greater decrease in body weight ($p < 0.01$) than placebo, with no group differences for MM and FM ΔFM ~ 2.4 kg = above MDC

Note: Body composition terminology was used as in the original paper.
Abbreviations: BC, body composition; BIA, bioelectrical impedance analysis; DXA, dual-energy x-ray absorptiometry; FFM, fat-free mass; FM, fat mass; LBM, lean body mass; LCD, low-caloric diet; LEKT, low-energy ketogenic therapy; LM, lean mass; LST, lean soft tissue; MDC, minimal detectable change (1 kg of FM for BIA and DXA); MM, muscle mass.

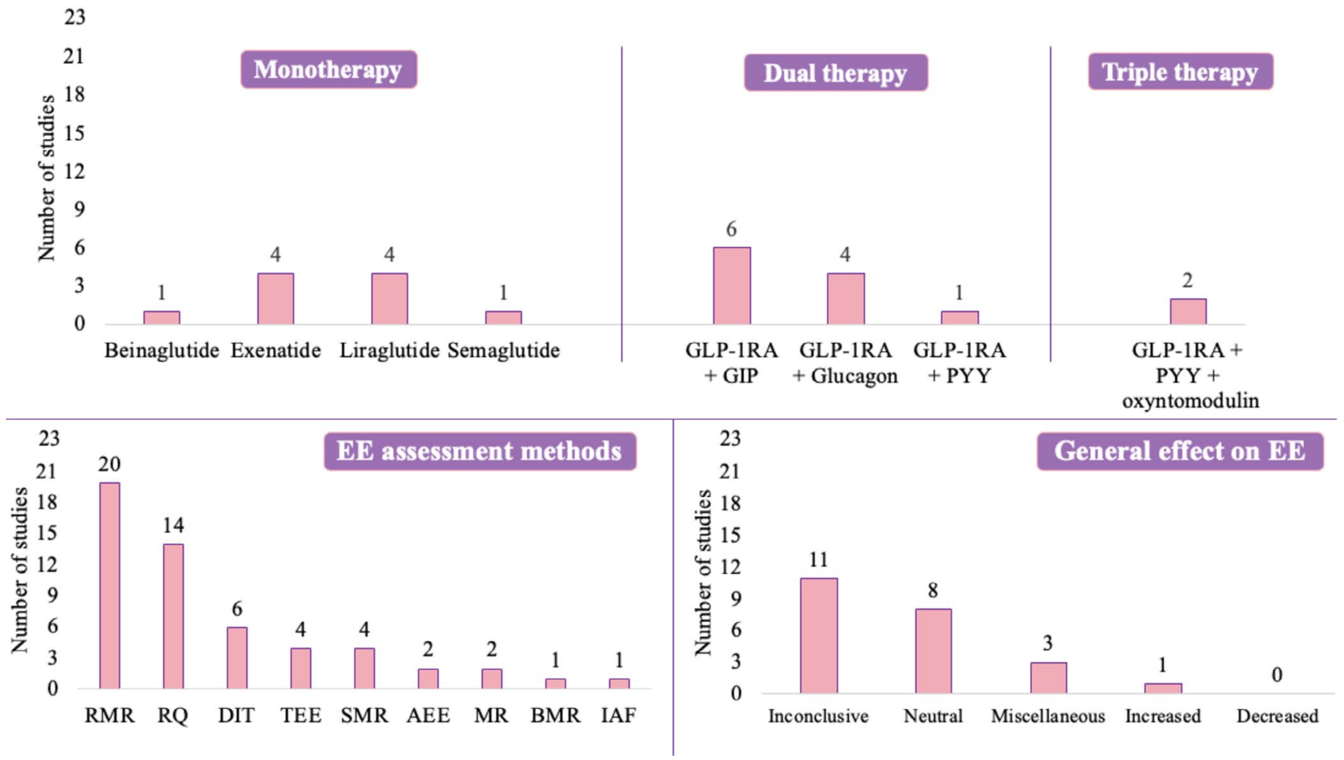

FIGURE 3 | Representation of glucagon-like peptide-1 receptor agonists mono and combination therapy, energy expenditure assessment methods, and general effect on energy expenditure of studies included in this scoping review (n = 23). AEE, activity energy expenditure; BMR, basal metabolic rate; DIT, diet-induced thermogenesis; EE, energy expenditure; GIP, glucose-dependent insulinotropic polypeptide; GLP-1RA, glucagon-like peptide-1 receptor agonist; IAF, inactive, awake, and fed thermogenesis; MR, macronutrient rates; PYY, peptide YY; RMR, resting energy expenditure; RQ, respiratory quotient; SMR, sleeping metabolic rate. Neutral effect: No changes in EE or subcomponents. Miscellaneous effect: Another effect in EE other than increase/decrease (n = 1, lower decrease in SMR compared to controls and a decrease in RQ; n = 1, decrease in RQ and increase in fat utilization; n = 1, increase in RQ). Inconclusive: Did not consider body weight/composition; original conclusions were neutral (n = 5), decreased (n = 4), and miscellaneous (n = 1, decrease in RQ; n = 1, decrease in RQ and an increase in fat oxidation).

3.4 | Mass-Dependent Effects on Energy Expenditure (N = 13)

Two trials investigated the effects of dual therapies using a WRIC, and both found miscellaneous effects on EE [20, 50]. Corbin et al. [50] after a 19-day intervention with a combination therapy with glucagon (0.2 mg daily) found a smaller decrease in SMR compared to controls and a decrease in RQ (indicating more fat oxidation), even after adjustments for body composition changes. No other differences were identified on RMR, TEE, BMR, and DIT [50]. Ravussin et al. [20] after an 18-week intervention with a combination therapy with GIP (i.e., tirzepatide 15 mg weekly) found a decrease in RQ but also an increase in fat utilization and decrease in both carbohydrate and protein utilizations following adjustments for body composition. No other differences were identified on RMR, TEE, and SMR [20].

Four trials found neutral effects of the interventions on the assessed EE variables after adjustments for body composition, including Basolo et al. [36] (WRIC) and Janssen et al. [38], which had EE as primary outcome: TEE [36] (WRIC), RMR [37, 38, 52], RQ [37, 38], DIT [36, 46, 52], AEE [36, 52], and SMR [36]. Exenatide was investigated in two of these studies using 20 mcg daily for 24 weeks [36] or 2 mg weekly for 12 weeks [38], liraglutide in 1 (1.8 mg/day for 26 weeks) [37], and another used a combination of GLP-1 with PYY and oxyntomodulin (4, 0.4, and 4 pmol/kg/min, respectively) for 12 h/day for 4 weeks [52].

Six studies using GLP-1RA monotherapy (exenatide, liraglutide, semaglutide, or beinaglutide) [39, 41, 53–56] and one using a combination therapy with GIP (tirzepatide) [57] for 12 weeks to 12 months were deemed inconclusive due to the applied statistical analyses. Majority of the studies performed only separate within- and/or between-group comparisons with no adjustments for body weight/composition changes over time [39, 41, 53–57]. Even though Van Ruiten et al. [53] applied a more comprehensive statistical approach (i.e., linear mixed model), body weight/composition changes were also not added to the model. Their proposed results on EE were neutral effects [41, 53, 54], decreased [39, 56, 57], and miscellaneous (increased fat oxidation and decrease in RQ and carbohydrate oxidation) [55].

3.5 | Mass-Independent Effects on Energy Expenditure (N = 10)

An acute intervention combining GLP-1 and glucagon for 45 min resulted in an increase in RMR at 90 min (45 min after infusion stopped). Notably, this increase was also followed by an increase

TABLE 3 | Summary of the mass-dependent effects* of glucagon-like peptide-1 receptor agonists mono and combination therapy on energy expenditure of studies included in this scoping review ($n = 13$).

Author, year	Intervention	Method of EE measurement and precision	EE components and specific methods	Data analysis	Baseline	After intervention/ comparator	Adaptive thermogenesis and energy balance	Conclusion
Monotherapy: GLP-1RA								
Basolo et al. 2018 [36]	Exenatide vs. placebo	Whole-room indirect calorimetry (baseline and week 24) Precision not discussed	TEE—23.25 h SMR—between 23:30 and 05:00 DIT*—awake fed thermogenesis: difference between EE in inactive state and SMR AEE—spontaneous physical activity measured by a radar system	*Analysis* ANCOVA *Covariates* Age, sex, race, chamber temperature, FM, and FFM	**TEE change** (baseline vs. week 24) Exenatide: −87 kcal (95% CI not provided), $p = 0.14$		**AT** and **EB** could not be calculated Missing absolute EE (pre and post) and BC (post) data	**Neutral effect** Exenatide: No changes in TEE, SMR, DIT and AEE after adjustments for body composition
van Eyk et al. 2020 [37]	Liraglutide vs. Placebo	Indirect calorimetry (baseline and Weeks 4, 12, and 26) Precision not discussed	RMR—duration of measurement not discussed RQ	*Analysis* ANCOVA *Covariates* LBM	**RMR** change (baseline vs. week 26) Liraglutide: −52 ± 128 kcal Placebo: +44 ± 144 kcal **RQ** Data expressed in graphs		**AT** could not be calculated: missing absolute EE data (pre and post) **EB** Liraglutide: −20,460 kcal (calculated based on 2.2 kg of FM loss); −2310 kcal (calculated based on 2.1 kg of LBM loss) = −22,770 kcal Placebo: +3930 kcal (calculated based on 0.3 kg of FM gain); −220 kcal (calculated based on 0.2 kg of LBM loss) = +3710 kcal	**Neutral effect** Liraglutide: Decrease in RMR at Week 4, but no changes in RMR at Week 12 or 26 ($p = 0.06$) and RQ after adjustments for body composition at Week 26
Janssen et al. 2020 [38]	Exenatide	Indirect calorimetry (baseline and Week 12) Precision not discussed	RMR—30 min RQ	*Analysis* Two-way mixed ANOVA *Covariates* Ethnicity, LM	Data expressed in graphs		**AT** could not be calculated: missing absolute EE data (pre and post) **EB:** −3720 kcal (calculated based on 0.4 kg of FM loss); −1100 kcal (calculated based on 1.0 kg of LM loss) = −4820 kcal	**Neutral effect** Exenatide: No changes in RMR or RQ after adjustments for body composition

(Continues)

TABLE 3 | (Continued)

Author, year	Intervention	Method of EE measurement and precision	EE components and specific methods	Data analysis	Baseline	After intervention/comparator	Adaptive thermogenesis and energy balance	Conclusion
Rodgers et al. 2021 [39]	Exenatide vs. placebo + hypocaloric diet	Indirect calorimetry (baseline and week 12) Precision not discussed	RMR—duration of measurement not discussed DIT—assessed with liquid meal tolerance test	*Analysis* Wilcoxon test *Covariates* None	**RMR** Exenatide: 1548.9 ± 224.4 kcal Diet: 1542.5 ± 194.6 kcal **DIT** Exenatide: 4.4 ± 2.0 Diet: 4.5 ± 2.0	**RMR** Exenatide: 1411.0 ± 184.5 kcal Diet: 1386.6 ± 116.9 kcal **DIT** Exenatide: 3.5 ± 2.4 Diet: 4.1 ± 2.0	**AT** Exenatide: Pre: 1548.9 (mRMR)—1605.1 (pRMR) = −56.2 kcal Post: 1411.0 (mRMR)—1519.7 (pRMR) = −108.7 kcal Δ AT exenatide: −52.5 kcal Diet: Pre: 1542.5 (mRMR)—1613.1 (pRMR) = −70.6 kcal Post: 1411.0 (mRMR)—1519.7 (pRMR) = −108.7 kcal Δ AT diet: −38.1 kcal **EB** Exenatide: −28,459.9 kcal (calculated based on 3.1 kg of FM loss); −3520 kcal (calculated based on 3.2 kg of FFM loss) = −31,979.9 Diet: −43,710 kcal (calculated based on 4.7 kg of FM loss); −2640 kcal (calculated based on 2.4 kg of FFM loss) = −46,350 kcal	**Inconclusive** (Decreased EE) Exenatide and hypocaloric diet: Decreased RMR ($p < 0.001$) Exenatide: Decreased DIT ($p = 0.04$)
Van Ruiten et al. 2022 [53]	Exenatide vs. dapagliflozin vs. exenatide + dapagliflozin vs. placebo	Indirect calorimetry (Day 10 and Week 16) Precision not discussed	RMR—30 min RQ	*Analysis* Linear mixed model *Covariates*: Baseline	**RMR** change (baseline vs. week 16) Exenatide: −45.0 ± 94.5 kcal Dapagliflozin: −44.6 ± 90.6 kcal Exenatide + dapagliflozin: −152.9 ± 92.6 kcal **RQ** Exenatide: +0.03 ± 0.04 Dapagliflozin: −0.03 ± 0.03 Exenatide + dapagliflozin: +0.01 ± 0.03		**AT** could not be calculated: Missing absolute EE data (pre and post) **EB** Exenatide: −24,180 kcal (calculated based on 2.6 kg of FM loss); +2640 kcal (calculated based on 1.2 kg of FFM gain) = −21,540 kcal Dapagliflozin: −24,645 kcal (calculated based on 2.7 kg of FM loss); +440 kcal (calculated based on 0.2 kg of FFM gain) = −24,205 kcal Exenatide + dapagliflozin: −34,410 kcal (calculated based on 3.7 kg of FM loss); +1980 kcal (calculated based on 0.9 kg of FFM gain) = −32,430 kcal	**Inconclusive** (Neutral effect) Exenatide or exenatide + dapagliflozin: No difference in RMR and RQ as compared to placebo

(Continues)

TABLE 3 | (Continued)

Author, year	Intervention	Method of EE measurement and precision	EE components and specific methods	Data analysis	Baseline	After intervention/comparator	Adaptive thermogenesis and energy balance	Conclusion
Silver et al. 2023 [41]	Liraglutide + placebo vs. sitagliptin + placebo vs. hypocaloric diet	Indirect calorimetry (baseline and Week 16) Precision not discussed	RMR—25 to 30 min, with 5–10 min of calibration prior RQ	*Analysis* Wilcoxon test or Kruskal–Wallis test *Covariates* None	**RMR** Liraglutide: 1755.4 ± 353.5 kcal Sitagliptin: 1853.7 ± 394.1 kcal Diet: 1833.2 ± 396.1 kcal **RQ** Liraglutide: 0.82 ± 0.06 Sitagliptin: 0.81 ± 0.06 Diet: 0.81 ± 0.04	**RMR** Liraglutide: 1670.9 ± 329.2 kcal Sitagliptin: 1711.9 ± 452.0 kcal Diet: 1767.3 ± 402.6 kcal **RQ** Liraglutide: 0.81 ± 0.05 Sitagliptin: 0.81 ± 0.05 Diet: 0.80 ± 0.06	**AT** Liraglutide: Pre: 1755.4 (mRMR)—1623.8 (pRMR) = +131.6 kcal Post: 1670.9 (mRMR)—1602.5 (pRMR) = +68.4 kcal Δ AT liraglutide: −63.2 kcal Sitagliptin: Pre: 1853.7 (mRMR)—1728.0 (pRMR) = +125.7 kcal Post: 1711.9 (mRMR)—1711.9 (pRMR) = 0 kcal Δ AT sitagliptin: −125.7 kcal Diet Pre: 1833.2 (mRMR)—1687.9 (pRMR) = +145.3 kcal Post: 1767.3 (mRMR)—1706.6 (pRMR) = +60.7 kcal Δ AT diet: −84.6 kcal **EB** Liraglutide: −21,390 kcal (calculated based on 2.3 kg of FM loss); −880 kcal (calculated based on 0.8 kg of LM loss) = −25,270 kcal Sitagliptin: +22,270 kcal (calculated based on 1.7 kg of FM gain); −660 kcal (calculated based on 0.6 kg of LM loss) = +21,610 kcal Diet: −21,390 kcal (calculated based on 2.3 kg of FM loss); +1540 kcal (calculated based on 0.7 kg of LM gain) = −19,850 kcal	**Inconclusive** (Neutral effect) Liraglutide: No changes in RMR and RQ
Alissou et al. 2025 [54]	Semaglutide	Indirect calorimetry (baseline, Months 7 and 12) Precision not discussed	RMR—30 min	Friedman test with Dunn's multiple post hoc test *Covariates* None	Absolute values expressed in graphs **RMR** Baseline vs. month 7: −244 kcal Month 7 vs. 12: +140 kcal **RMR/LM** Month 7: 33.48 ± 4.50 kcal/kg Month 12: 36.14 ± 5.13 kcal/kg		**AT** could not be calculated: missing absolute EE data (pre and post) **EB**: −112,530 kcal (calculated based on −12.1 kg of FM loss); −3597 kcal (calculated based on −3.27 kg of LM loss) = −116,127 kcal	**Inconclusive** (Neutral effect) RMR decreased until month 7 ($p < 0.0001$) and increased in month 12 ($p < 0.05$). No difference from baseline to month 12. RMR/LM increased from Months 7 to 12 ($p < 0.05$)

(Continues)

TABLE 3 | (Continued)

Author, year	Intervention	Method of EE measurement and precision	EE components and specific methods	Data analysis	Baseline	After intervention/ comparator	Adaptive thermogenesis and energy balance	Conclusion
Basolo et al. 2025 [55]	Liraglutide	Whole-room indirect calorimetry (baseline and Month 6) Recovery rates within 5% of stoichiometric expectations	TEE—24 h 24hSMR—measured between 23:30 and 5:00 and extrapolated to 24 h EE_0—inactive, awake and fed state over 15 h DIT—awake and fed thermogenesis over 15 h RQ Macronutrient oxidation rates	Paired *t*-test *Covariates*: None	**TEE** 1857 ± 364 kcal **24hSMR:** 1281 ± 314 kcal **EE_0**: 1218 ± 212 kcal **DIT:** 412 ± 83 kcal **RQ:** 0.86 ± 0.06 **Macronutrient oxidation:** Fat: 668 ± 417 kcal Carb: 896 ± 343 kcal Protein:324 ± 112 kcal	**TEE** 1874 ± 361 kcal **24hSMR:** 1342 ± 306 kcal **EE_0**: 1188 ± 221 kcal **DIT:** 356 ± 114 kcal **RQ:** 0.79 ± 0.04 **Macronutrient oxidation:** Fat: 1021 ± 361 kcal Carb: 474 ± 220 kcal Protein: 354 ± 129 kcal	**AT*** 1874 (mTEE) − 1833 (pTEE) = +42 kcal; no evidence of AT (95% CI: −88 to +172, $p = 0.49$) *Extracted from the article—pTEE was obtained by linear regression analysis and confirmed by a linear mixed-effects model with adjustments **EB:** −80,910 kcal (calculated based on −8.7 kg of FM loss); −1870 kcal (calculated based on −1.7 kg of LST loss) = −82,780 kcal	**Inconclusive** (Miscellaneous effect) Liraglutide increased fat oxidation and decreased carb oxidation and RQ ($p < 0.05$) No changes in TEE, 24hSMR, EE_0, DIT, and protein oxidation
Liu et al. 2025 [56]	Beinaglutide	Indirect calorimetry (baseline, Week 4, and Week 12) Precision not discussed	RMR	Paired *t*-test and repeated one-way ANOVA *Covariates* None	**RMR:** 1644.9 ± 228.9 kcal	**RMR:** Week 4 1566 ± 240.1 kcal Week 12 1549.4 ± 228.9 kcal	**AT** and **EB** could not be calculated Missing absolute FFM data (pre and post)	**Inconclusive** (Decreased EE) Beinaglutide decreased RMR at week 12 ($p = 0.034$)
Dual therapy: GLP-1RA and another drug								
Corbin et al. 2023 [50]	GLP-1 + glucagon + hypocaloric diet vs. placebo + hypocaloric diet	Whole-room indirect calorimetry (baseline and Day 19) Coefficient of variation was calculated for each variable (data not available)	TEE—23 h RMR—between 08:00 to 09:00 SMR—measured between 00:00 to 05:00 BMR—measured after 8+ h of sleep, and 12–14 h of fasting DIT—measured following breakfast with BMR subtracted RQ	*Analysis* Multivariate ANOVA *Covariates* FM, FFM	**RQ** Both groups combined: 0.89 (no standard deviation provided) **TEE, RMR, SMR, BMR, DIT:** data expressed in graphs	**RQ** GLP-1 + glucagon: 0.80 ± 0.03 Diet: 0.85 ± 0.02 **TEE, RMR, SMR, BMR, DIT:** data expressed in graphs	**AT** could not be calculated: missing absolute EE data (pre and post) **EB** Exenatide: −13,950 kcal (calculated based on 1.5 kg of FM loss); −2640 kcal (calculated based on 2.4 kg of FFM loss) = −16,590 kcal Diet: −9300 kcal (calculated based on 1.0 kg of FM loss); −1980 kcal (calculated based on 1.8 kg of FFM loss) = −11,280 kcal	Miscellaneous effect GLP-1 + glucagon: Lower decrease in SMR when compared to diet and decrease in RQ, even after adjusting for body composition changes No changes in TEE, RMR, BMR, and DIT after adjustments for body composition

(Continues)

TABLE 3 | (Continued)

Author, year	Intervention	Method of EE measurement and precision	EE components and specific methods	Data analysis	Baseline	After intervention/comparator	Adaptive thermogenesis and energy balance	Conclusion
Ravussin et al. 2025 [20]	Tirzepatide	Whole-room indirect calorimetry for two consecutive days (average) (baseline and Week 18) Precision not discussed	TEE—23 h RMR—measured between 06:30–7:00 SMR—measured between 02:00–05:00 and extrapolated for 24 h RQ Macronutrient utilization rates	ANCOVA *Covariates*: Treatment, baseline values, changes in FM and FFM *Post hoc additional covariates*: Baseline FM and FFM, and estimated average daily energy imbalance	**TEE** Tirzepatide: 2311.7 ± 408.8 kcal Placebo: 2269.9 ± 365.9 kcal **RMR** Tirzepatide: 1807.2 ± 320.9 kcal Placebo: 1760.7 ± 273.1 kcal **SMR** Tirzepatide: 1687.6 ± 302.4 kcal Placebo: 1628.9 ± 245.1 kcal **RQ** Tirzepatide: 0.86 ± 0.02 Placebo: 0.86 ± 0.02 **Macronutrient utilization (g/1000 kcal EE/day)** Tirzepatide: Fat: 38.7 ± 8.7 Carb: 113.4 ± 17.9 Protein: 36.3 ± 5.5 Placebo: Fat: 36.4 ± 8.2 Carb: 120.5 ± 15.8 Protein: 34.4 ± 6.2	**TEE** Tirzepatide: 1870.6 ± 349.5 kcal Placebo: 2065.4 ± 307.3 kcal **RMR** Tirzepatide: 1541.9 ± 290.7 kcal Placebo: 1643.7 ± 237.2 kcal **SMR** Tirzepatide: 1466.2 ± 255.7 kcal Placebo: 1521.5 ± 216.0 kcal **RQ** Tirzepatide: 0.83 ± 0.04 Placebo: 0.87 ± 0.02 **Macronutrient utilization (g/1000 kcal EE/day)** Tirzepatide: Fat: 51.4 ± 14.1 Carb: 92.3 ± 27.1 Protein: 28.8 ± 7.2 Placebo: Fat: 34.6 ± 8.1 Carb: 123.8 ± 15.5 Protein: 35.3 ± 5.4	**AT** Tirzepatide: Pre: 1807.2 (mRMR)—1658.53 (pRMR) = +148.67 kcal Post: 1541.9 (mRMR)—1501 kcal (pRMR) = +40.9 kcal Δ AT Tirzepatide: −107.77 kcal Placebo: Pre: 1760.7 (mRMR) −1650.5 (pRMR) = +110.2 kcal Post: 1643.7 (mRMR)—1586.44 (pRMR) = +57.26 kcal Δ AT placebo: −52.94 kcal **EB** Tirzepatide: −108,810 kcal (calculated based on −11.7 kg of FM loss); −6490 kcal (calculated based on −5.9 kg of FFM loss) = −115,300 kcal Placebo: −65,100 kcal (calculated based on −7.0 kg of FM loss); −2640 kcal (calculated based on −2.4 kg of FFM loss) = −67,740 kcal	**Miscellaneous effect on EE** Tirzepatide decreased RQ ($p < 0.0001$); there was an increase in fat utilization ($p < 0.0001$), and a decrease in both carb and protein utilization ($p < 0.001$) No differences in TEE, RMR, and SMR between groups after adjustments for body composition at Week 18

(Continues)

TABLE 3 | (Continued)

Author, year	Intervention	Method of EE measurement and precision	EE components and specific methods	Data analysis	Baseline	After intervention/comparator	Adaptive thermogenesis and energy balance	Conclusion
Schiavo et al. 2025 [57]	Tirzepatide + LEKT vs. tirzepatide + LCD	Indirect calorimetry (baseline and Week 12) Precision not discussed	RMR—15 min	Mann–Whitney test Paired *t*-test *Covariates* None	**RMR** LEKT: 1716 ± 317 kcal LCD: 1769 ± 235 kcal	**RMR** LEKT: −1.2% ± 0.9% (1695.4 kcal*) LCD: −5.3% ± 1.8% (1675.2 kcal*) *Calculated from % decreased	**AT** LEKT: Pre: 1716 (mRMR)—1792.03 (pRMR) = −76.03 kcal Post: 1695.4 (mRMR)—1784.02 (pRMR) = −88.62 kcal Δ AT LEKT: −12.59 kcal LCD: Pre: 1769 (mRMR)—1810.72 (pRMR) = −41.72 kcal Post: 1675.2 (mRMR)—1741.3 (pRMR) = −66.1 kcal Δ AT LCD: −24.38 kcal **EB** LEKT: −70,680 kcal (calculated based on −7.6 kg of FM loss); −330 kcal (calculated based on −0.3 kg of FFM loss) = −71,010 kcal LCD: −55,800 kcal (calculated based on −6.0 kg of FM loss); −2860 kcal (calculated based on −2.6 kg of FFM loss) = −58,660 kcal	**Inconclusive** (Decreased EE) At Week 12, only the tirzepatide + LCD reduced RMR ($p < 0.001$). Tirzepatide + LEKT presented a smaller % decrease in RMR ($p = 0.019$)

(Continues)

TABLE 3 | (Continued)

Author, year	Intervention	Method of EE measurement and precision	EE components and specific methods	Data analysis	Baseline	After intervention/ comparator	Adaptive thermogenesis and energy balance	Conclusion
Triple therapy: GLP-1RA in combination with two other drugs								
Behary et al. 2019 [52]	GLP-1 + PYY + oxyntomodulin vs. placebo	Indirect calorimetry (baseline and Week 4) Precision not discussed	RMR—15-20 min DIT—15-20 min after 30 min of ingestion of a mixed meal test AEE (accelerometry)	*Analysis* ANCOVA *Covariates* Body weight, MM	**RMR** Intervention: 1984.3 kcal Placebo: 1936.2 kcal **DIT** Intervention: 120.6 kcal Placebo: 229.5 kcal **AEE** Intervention: 626.7 kcal Placebo: 653.8 kcal (no standard deviation provided)	**RMR** Intervention: 1780.2 kcal Placebo: 1891.4 kcal **DIT** Intervention: 118.6 kcal Placebo: 63.7 kcal **AEE** Intervention: 688.2 kcal Placebo: 530.7 kcal (no standard deviation provided)	**AT** Intervention Pre: 1984.3 (mRMR)—1882.8 (pRMR) = +101.5 kcal Post: 1780.2 (mRMR)—1837.4 (pRMR) = −57.2 kcal Δ AT intervention: −158.7 kcal Placebo: Pre: 1936.2 (mRMR)—1989.6 (pRMR) = −53.4 kcal Post: 1891.4 (mRMR)—1965.6 (pRMR) = −74.2 kcal Δ AT placebo: −20.8 kcal **EB** Intervention: −23,250 kcal (calculated based on 2.5 kg of FM loss); −1870 kcal (calculated based on 1.7 kg of MM loss) = −25,120 kcal Placebo: −12,090 kcal (calculated based on 1.3 kg of FM loss); −990 kcal (calculated based on 0.9 kg of MM loss) = −13,080 kcal	Neutral effect GLP-1 + PYY + oxyntomodulin: No changes in RMR, DIT, or AEE after adjustments for body weight and composition

Note: Neutral effect: No changes in EE or subcomponents. Miscellaneous effect: Another effect in EE other than a direct increase/decrease. Body composition terminology was used as in the original paper.
Abbreviations: AEE, activity energy expenditure; ANCOVA, analysis of covariance; ANOVA, analysis of variance; AT, adaptive thermogenesis (pre vs. post RMR/FFM); BMR, basal metabolic rate; Carb, carbohydrate; DIT, diet-induced thermogenesis; EB, energy balance (9.3 kcal/g FM loss, 1.1 kcal/g FFM loss; 13.1 kcal/g FM gain, 2.2 kcal/g FFM gain); EE, energy expenditure; EE_0, estimated as the y-intercept of the regression line plotting energy expenditure against spontaneous physical activity, and extrapolated over a 15-h period; FFM, fat-free mass; FM, fat mass; GLP-1, glucagon-like peptide-1; LBM, lean body mass; LCD, low-caloric diet; LEKT, low-energy ketogenic therapy; LM, lean mass; LST, lean soft tissue; MM, muscle mass; mRMR, measured resting metabolic rate; pRMR, predicted resting metabolic rate (26.7 × FFM + 192.7); PYY, peptide YY; RMR, resting metabolic rate; RQ, respiratory quotient; SMR, sleeping metabolic rate; TEE, total energy expenditure.

TABLE 4 | Summary of the mass-independent effects[a] of glucagon-like peptide-1 receptor agonists mono and combination therapy on energy expenditure of studies included in this scoping review ($n = 10$).

Author, year	Intervention	Method of EE measurement and precision	EE components	Data analysis	Baseline	After intervention/ comparator	Conclusion
Monotherapy: GLP-1RA							
Etoga et al. 2023 [40]	Liraglutide vs. vildagliptin	Indirect calorimetry (baseline and Week 2) Precision not discussed	RMR—20 min, with 10 min of calibration prior	*Analysis* Wilcoxon test and Mann–Whitney *U* test *Covariates* None	Liraglutide: Median 1699 kcal (IQR 1426–1771) Vildagliptin: Median 1382 kcal (IQR 1540–1771)	Liraglutide: Median 1454 (IQR 1377–1590) Vildagliptin: Median 1598 (IQR 1138–1714)	**Inconclusive** (Decreased EE) Liraglutide: Decreased pre-post RMR ($p = 0.02$) No between-group differences
Dual therapy: GLP-1RA and another drug							
Daousi et al. 2009 [42]	GLP-1 vs. GIP vs. GLP-1 + GIP vs. dextrose	Indirect calorimetry (baseline and 4 h) Precision not discussed	RMR—20 min, with 5 min of calibration prior. Repeated every hour of infusion **RQ**	*Analysis* Paired *t*-test or Wilcoxon test and general linear model *Covariates* None	**RMR** Obesity + T2DM: 2251.2 ± 57.8 kcal Healthy participants: 1674.5 ± 34.7 kcal **RQ** Data not reported	**RMR** Obesity + T2DM: GLP-1: 2118.4 ± 131.7 kcal GIP: 2256.4 ± 148.6 kcal GLP-1 + GIP: 2179.2 ± 69.6 kcal Dextrose: 2236.0 ± 112.9 kcal Healthy participants: GLP-1: 1633.3 ± 64.0 kcal GIP: 1613.6 ± 54.5 kcal GLP-1 + GIP: 1630.2 ± 51.0 kcal Dextrose: 1632.6 ± 69.1 kcal **RQ** Data not reported	**Neutral effect** GLP-1 or GLP-1 + GIP: No changes in RMR and RQ GIP: Decreased RMR in healthy group

(Continues)

TABLE 4 | (Continued)

Author, year	Intervention	Method of EE measurement and precision	EE components	Data analysis	Baseline	After intervention/comparator	Conclusion
Tan et al. 2013 [43]	GLP-1 vs. glucagon vs. GLP-1 + glucagon vs. placebo	Indirect calorimetry (baseline, 45 min, and 90 min) Precision not discussed	RMR—15 min, with 30 min of calibration prior RQ	*Analysis* Linear mixed model *Covariates* Weight	**RMR** GLP-1: 1487 ± 65.9 kcal Glucagon: 1469 ± 66.0 kcal GLP-1 + Glucagon: 1485 ± 67.4 kcal Placebo: 1487 ± 70.9 kcal **RQ** GLP-1: 0.857 ± 0.018 Glucagon: 0.851 ± 0.02 GLP-1 + glucagon: 0.834 ± 0.022 Placebo: 0.822 ± 0.018	**RMR change** GLP-1 vs. placebo: +2.47 (95% CI 63.49, 68.43) Glucagon vs. placebo: +146.99 (95% CI 83.75, 210.24) GLP-1 + glucagon vs. placebo: +146.26 (95% CI 82.58, 209.95) **RQ change** GLP-1 vs. placebo: +0.02 (95% CI 0.01, 0.06) Glucagon vs. placebo: +0.03 (95% CI 0.003, 0.07) GLP-1 + glucagon vs. placebo: +0.07 (95% CI 0.03, 0.10)	**Increased EE** GLP-1 + glucagon and glucagon increased RMR ($p < 0.001$ for both) and RQ ($p = 0.03$, $p < 0.001$, respectively)
Cegla et al. 2014 [44]	GLP-1 vs. glucagon vs. GLP-1 + glucagon vs. placebo	Indirect calorimetry (baseline and 40 min) Precision not discussed	RMR—10 min, with 20 min of calibration prior RQ	*Analysis* Area under the curve + one-way repeated-measures ANOVA + Tukey post hoc *Covariates* None	Data expressed in graphs		**Miscellaneous effect** GLP-1 + glucagon and glucagon increased RQ ($p < 0.001$ and < 0.01 respectively) but produced only a trend towards increased RMR ($p > 0.05$). GLP-1 did not produce any changes in RMR or RQ

(Continues)

TABLE 4 | (Continued)

Author, year	Intervention	Method of EE measurement and precision	EE components	Data analysis	Baseline	After intervention/ comparator	Conclusion
Schmidt et al. 2014 [45]	GLP-1 vs. PYY vs. GLP-1 + PYY vs. placebo	Indirect calorimetry (baseline, 30 min, 60 min, 90 min, 120 min, 150 min) Precision not discussed	RMR—15 min, with 5 min of calibration prior. Repeated every 30 min RQ	*Analysis* Linear mixed model *Covariates* None	Data not reported		**Neutral effect** No overall treatment effect for RMR and RQ
Bagger et al. 2015 [46]	GLP-1 vs. glucagon vs. oxyntomodulin vs. GLP-1 + glucagon vs. Placebo	Indirect calorimetry (baseline and 4 h) Precision not discussed	DIT—liquid meal test, measured over 20 min at start and end of infusion	*Analysis* Linear mixed model *Covariates* None	Data expressed in graphs		**Neutral effect** No significant changes in DIT with any of the interventions
Bergmann et al. 2019 [47]	IIGI+ GLP-1 vs. IIGI + GIP vs. IIGI + GLP-1 + GIP vs. IIGI + placebo	Indirect calorimetry (baseline and 210 min) Precision not discussed	RMR—15 min RQ	*Analysis* One-way repeated measures ANOVA and linear mixed model *Covariates* None	Data not reported	**RMR** Data not reported **RQ** IIGI+GLP-1: 0.96 ± 0.02 IIGI+GIP: 0.83 ± 0.01 IIGI+GIP + GLP-1: 0.92 ± 0.02IIGI+ placebo: 0.83 ± 0.02	**Neutral effect** GLP-1 and GLP-1 + GIP: No changes in RMR. Increased RQ post-intervention ($p < 0.001$)—authors attributed to differences in glucose administered
Bergmann et al. 2020 [48]	Background GLP-1RA + GIP vs. placebo	Indirect calorimetry (baseline, 45 min, and 250 min) Precision not discussed	RMR—15 min RQ	*Analysis* Paired *t*-test *Covariate* None	**RMR** GLP-1RA + GIP: 1790 ± 41 kcalPlacebo: 1747 ± 42 kcal **RQ** GIP: 0.83 ± 0.01 Placebo: 0.84 ± 0.02	**RMR** GLP-1RA + GIP: 1799 ± 54 kcal Placebo: 1777 ± 52 kcal **RQ** GIP: 0.82 ± 0.01 Placebo: 0.86 ± 0.01	**Inconclusive** (Miscellaneous effect) GLP-1RA + GIP: No changes in RMR; but decreased RQ at 250 min ($p = 0.023$)

(Continues)

TABLE 4 | (Continued)

Author, year	Intervention	Method of EE measurement and precision	EE components	Data analysis	Baseline	After intervention/ comparator	Conclusion
Stensen et al. 2022 [49]	GLP-1 + GIPR antagonist GIP (3–30) vs. GLP-1 + placebo	Indirect calorimetry (baseline, 30 min, 90 min and 150 min) Precision not discussed	RMR—15 min RQ	*Analysis* Paired *t*-test or Wilcoxon test *Covariates* None	**RMR** GLP-1 + GIPR antagonist: Median 1794 kcal/d (IQR 2002–1497) GLP-1 + placebo: Median 1847 kcal/d (IQR 1670–2074) **RQ** GLP-1 + GIPR Antagonist: Median 0.85 (IQR 0.80–0.91) GLP-1 + placebo: Median 0.84 (IQR 0.77–0.89)	**RMR change** GLP-1 + GIPR antagonist: Median −110 (IQR 144 to −202) GLP-1 + placebo: Median −52 (IQR 255 to −82) **RQ** GLP-1 + GIPR antagonist: Median 0.81 (IQR 0.79–0.87) GLP-1 + placebo: Median 0.81 (IQR 0.78–0.93)	**Inconclusive** (Neutral effect) GLP-1 + GIP antagonist: No changes in RMR and RQ
Triple therapy: GLP-1RA in combination with two other drugs							
Tan et al. 2017 [51]	GLP-1 + PYY + oxyntomodulin vs. placebo	Indirect calorimetry (baseline and 210 min) Precision not discussed	RMR—15-20 min, with 10 min of calibration prior	*Analysis* Paired *t*-test *Covariates* None	**RMR change** Intervention: −4.6 ± 74.2 kcal Placebo: +22.0 ± 68.8 kcal		**Inconclusive** (Neutral effect) GLP-1 + PYY + oxyntomodulin: No changes in RMR

Note: Neutral effect: No changes in EE or subcomponents. Miscellaneous effect: Another effect in EE other than a direct increase/decrease.
Abbreviations: AEE, activity energy expenditure; ANOVA, analysis of variance; BMR, basal metabolic rate; DIT, diet-induced thermogenesis; EE, energy expenditure; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; IIGI, isoglycemic intravenous glucose infusion; PYY, peptide YY; RMR, resting metabolic rate; RQ, respiratory quotient; SEE, sleeping energy expenditure.
[a]Adaptive thermogenesis and energy balance were not calculated due to lack of body composition data and not significant weight/body composition changes post-intervention (intervention duration ranged from hours to 2 weeks).

in RQ (more carbohydrate oxidation) [43]. In contrast, another acute intervention combining GLP-1 and glucagon for 40 min found an increase in RQ but only a trend towards increased RMR [44].

Four studies evaluated the effects of GLP-1RA combination therapies—two with GIP [42, 47], one with glucagon [46], and one with PYY [45] for 2.5–4 h—and found neutral effects on RMR, RQ, and DIT. Of note, Bergmann et al. [47] found an increase in RQ post-intervention; however, the authors attributed it to differences in glucose administered.

Four trials were deemed inconclusive due to the analyses performed. Three involved interventions with dual or triple therapy (150–250 min) with only within-group comparisons (no comparison with controls) [48, 49, 51]. Their proposed results were neutral [49, 51] or miscellaneous impact on EE (no change in EE but decrease in RQ) [48]. Etoga et al. conducted a 2-week intervention with liraglutide and, despite not reporting weight loss, performed separate within- and between-group comparisons. They concluded that the intervention led to a decrease in RMR [40].

4 | Discussion

4.1 | Main Results

GLP-1RA mono or combination therapy does not appear to exert major effects on EE, especially on RMR, which was the most frequently investigated EE measure. These findings were consistent regardless of the presence of weight loss and whether the intervention was acute or chronic. However, combination therapies of GLP-1RA with glucagon or GIP show potential for influencing EE, especially macronutrient oxidation and utilization, which could support weight loss and the maintenance of the lost weight over time. GLP-1RA mono or combination therapy seems effective in promoting weight loss, followed by reductions in both FM and FFM.

4.2 | Update and Comparison With Previous GLP-1RA Monotherapy

The findings of our scoping review were largely consistent with the previous systematic review of GLP-1RA monotherapy [18]. The authors concluded that GLP-1, liraglutide, and exenatide tend to have neutral effects on EE. Only one trial in this review investigated semaglutide using the commonly indicated dose for diabetes management (1.0 mg/week) rather than obesity management (2.4 mg/week). Even with significant weight loss, this 12-week crossover trial concluded that semaglutide had a neutral effect on RMR after adjustments for lean mass (i.e., linear mixed model) [26].

Our updated review included studies that used exenatide, liraglutide, semaglutide, or beinaglutide (a medication approved in China) as GLP-1RA monotherapy and also found a neutral effect on EE, after considering the few studies that considered weight/body composition changes in their analyses. Notably, using WRIC, a more robust and precise methodology, a 24-week exenatide intervention produced neutral effects on TEE and subcomponents [36]. Also using WRIC, a 6-month liraglutide intervention identified improvements in macronutrient oxidation; however, these results need to be double-checked after proper adjustments [55].

Majority of the liraglutide trials used doses for diabetes management (1.2–1.8 mg/day) rather than recommended target dosage indicated for obesity management (3 mg/day) [58]. Additionally, exenatide is not currently indicated for the latter, and doses used were consistent with the maximum recommended dose for diabetes management [58]. There was only one additional study that investigated semaglutide, and it used the target dosage for obesity management (i.e., 2.4 mg/week); however, it produced inconclusive results. Studies focused on GLP-1RA monotherapy, especially with newer formulations such as semaglutide, and dosages targeting obesity management are needed to further understand its effect on EE during obesity pharmacological treatment. The effects of GLP-1RA mono or combination therapy on EE may be divided into mass-dependent and mass-independent effects, which include direct/indirect hormonal effects. Figure 4 summarizes these potential effects, which are discussed below.

4.3 | Mass-Dependent Effects of GLP-1RA Mono and Combination Therapy on EE

Chronic interventions using GLP-1RA mono or combination therapy resulted in negative energy balance and significant changes in weight/body composition. As a result of weight loss, which is intensified following GLP-1RA therapy, there are expected decreases in FFM, FM, organ metabolic rates, body temperature, and circulating hormone concentrations (e.g., leptin, T3, and insulin), ultimately leading to a decrease in EE [11]. FFM, which includes skeletal muscle mass and high-EE organs such as the liver, kidneys, and heart, is highly metabolically active; thus, a decrease in FFM due to weight loss favors a decrease in EE [12]. However, it is unclear whether decreases in organ masses are associated with reductions in specific oxidation rates. It seems that during a negative energy balance, the liver EE may increase rather than decrease [59]. Finally, decreases in organ/tissue oxygen consumption may not reflect a decrease in oxidative phosphorylation because energetic efficiency may increase with a decrease in oxygen consumption [60]. On a related note, AT may favor weight regain because an individual's EE may be disproportionately low compared to their new body composition, and accelerated FM gain may occur due to an imbalance between energy intake and EE [12, 61].

Evaluating changes in EE must consider changes in body composition. Included studies that reported weight loss evaluated body composition using mostly a two-component method (BIA: FFM and FM), and a few used a three-component method, such as DXA, which produces information beyond FM/FFM by measuring bone mineral content and then estimating FM and lean soft tissue. Notably, changes in hydration can still affect DXA estimates, and DXA should not be used as a proxy for skeletal muscle mass because lean soft tissue composition varies with weight loss. No studies have analyzed a multicomponent model in depth, which integrates the strengths of several independent body composition techniques to produce a more accurate estimate. These multicomponent

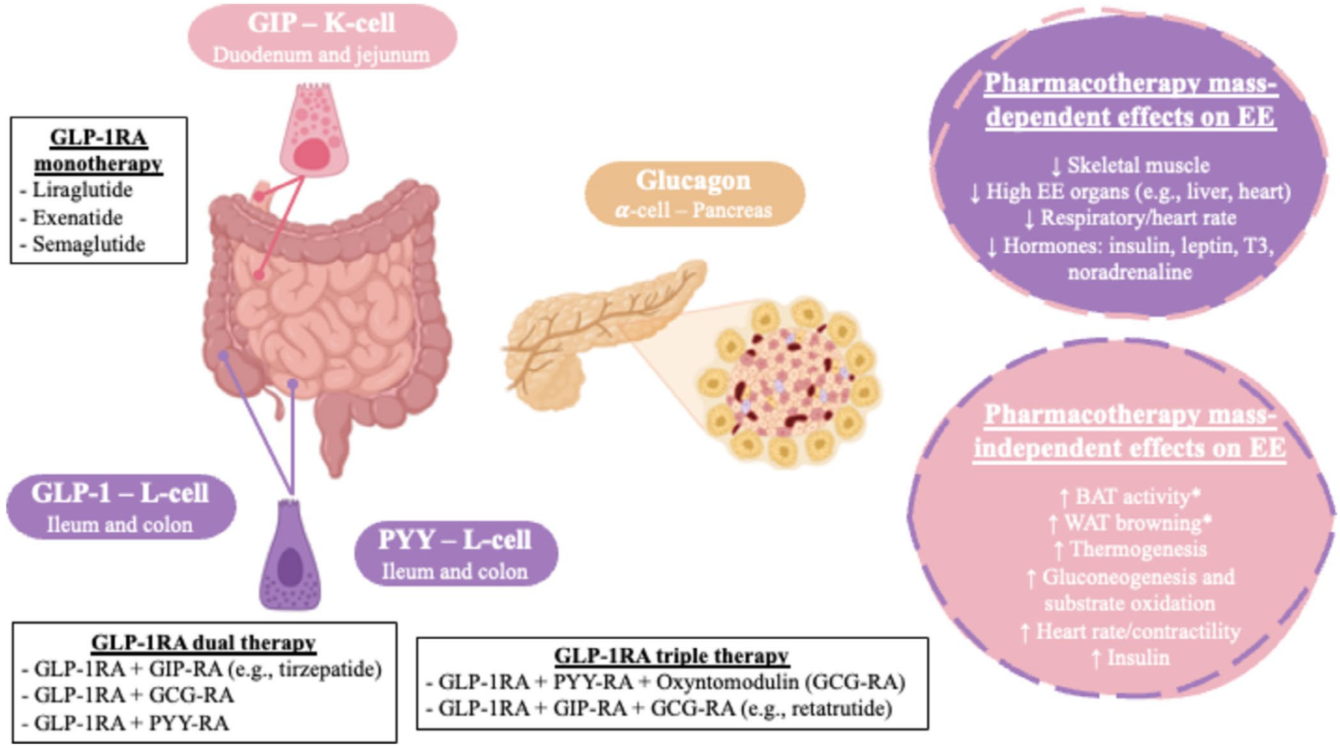

FIGURE 4 | Representation of common glucagon-like peptide-1 receptor agonists mono and combination therapies, target hormones, and potential effects on energy expenditure depending on the therapy. *Based on animal studies. BAT, brown adipose tissue; EE, energy expenditure; GCG, glucagon; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; PYY, peptide YY; RA, receptor agonist; T3, triiodothyronine; WAT, white adipose tissue.

models reduce the underlying assumptions that a two- or three-component method assumes, such as constant hydration, density, protein, and residual mass, accounting for the anatomical FFM composition and having lower minimal detectable change values. Additionally, none of the included studies evaluated organ masses (e.g., magnetic resonance imaging or computed tomography) that could be used to estimate specific metabolic rates; therefore, the specific contribution of high-metabolic-rate organs, such as the liver and brain, has not been explored. Given the potentially subtle effects of GLP-1RA mono or combination therapy on EE, employing more advanced body composition modeling could provide greater sensitivity [30]. This would enable a more accurate assessment of small but meaningful changes in mass-independent EE adaptations.

4.4 | Mass-Independent Effects of GLP-1RA Mono and Combination Therapy on EE

It seemed that some degree of AT might have occurred after the use of GLP-1RA mono or combination therapy. However, there was considerable variance in the methodological standards used to calculate AT; thus, the effects of GLP-1RA therapy on AT are still unclear. The general effect size of AT studies is approximately 100–150 kcal/day; the 6 studies in which AT was estimated reached similar values (i.e., ~50–150 kcal/day). Notably, the "Biggest Loser Study" identified a more pronounced effect size; however, this effect had been explained by a very pronounced weight loss, the combination of strict dieting plus extensive exercising, and methodological issues (i.e., measurements of RMR before and after weight loss could not be performed with the same device) [62]. Future GLP-1RA studies should focus on evaluating AT to generate further evidence.

The individual hormones or their combination may have a direct effect on EE and represent additional exploratory mechanisms impacting EE. GLP-1 is insulinotropic, and insulin has a multifaceted impact on EE, substrate metabolism, and energy storage, particularly through its interaction with adipose tissues and the central nervous system (e.g., hypothalamus). In general, insulin is not thermogenic. Insulin signaling in adipose and other peripheral tissues may indirectly inhibit uncoupling protein-1 expression in mitochondria, which is crucial for BAT activation, thermogenesis, and fat oxidation. Reduced energy intake and weight loss lead to a decrease in plasma insulin and, thus, a decrease in energy-consuming anabolic processes like lipogenesis [63–65].

Glucagon is a catabolic hormone involved in the mobilization of energy stores, and both acute and chronic agonism seem to increase EE [66]. In humans, glucagon increased EE independently of BAT activation and with a similar magnitude to cold activation [67]. Glucagon stimulates gluconeogenesis in the liver, an energy-consuming process that requires ATP, directly increasing EE, and also stimulates liver fat oxidation, inhibiting liver and muscle glycolysis. Glucagon may also act directly in the heart, increasing heart rate and contractility, ultimately leading to increases in EE [68, 69]. There is an additional effect of glucagon on urea production, which is also an energy-consuming process, fueled by the influx of amino acids from protein degradation and skeletal muscle wasting as precursors for gluconeogenesis [70, 71], further potentiated by losses in skeletal muscle mass with weight loss. Glucagon seems the most promising hormone to stimulate changes in EE independently and apparently does not require the presence of GLP-1RA for its effectiveness [43, 44]. Unlike GLP-1RA monotherapy, which acts mainly through insulin secretion and appetite suppression, GLP-1RA combined with glucagon engages complementary catabolic pathways that may increase EE and substrate utilization. However, low insulin levels may be required to stimulate thermogenesis, as in weight loss [65]. Of note, glucagon may lead to an increase in glycemia, but the combination with GLP-1 seems to protect against hyperglycemia [43]. Glucagon's chronic use should be cautiously considered, given the potential for muscle loss associated with medically used weight loss [72, 73]. In the clinical setting, the catabolic effect of glucagon can be monitored by an increase in urea production rate, which was not evaluated by the included studies.

GIP has synergistic effects with GLP-1RA [47]; it stimulates insulin and glucagon secretion and therefore may indirectly increase EE [74]. However, the combination of GLP-1RA and GIP has not shown a major impact on EE in humans. After a comprehensive WRIC assessment, chronic use of tirzepatide appeared to improve energy metabolism efficiency by increasing fat utilization and decreasing carbohydrate and protein utilization [20]. Acute co-infusions of GLP-1RA and GIP performed by Bergmann et al. found both a decrease [48] and an increase [47] in RQ, which can be explained by methodological variations. GIP receptor antagonism has also been explored with positive effects on weight loss [75, 76]; however, like GIP receptor agonism, it seems to produce a neutral effect on EE [49]. PYY does not seem to impact EE either when associated with GLP-1RA or, in triple therapy, with oxyntomodulin [51, 52]. Finally, GLP-1, glucagon, GIP, or PYY does not seem to have a direct impact on the concentration of hormones known to influence EE, such as T3. However, they might still indirectly influence these hormones through mass-dependent effects on weight loss and body composition alterations.

Notably, opposite effects of polyagonistic therapy may be pronounced depending on the context. Glucagon may boost EE during acute infusions, potentially reflecting transient shifts in substrate oxidation and catabolic response [43, 44, 65], whereas prolonged infusions (e.g., 72 h) [77] or longer interventions (e.g., 19 days) [50] may not produce the same effects. The difference between the acute and chronic effects of glucagon may be explained by an adaptation in metabolism induced by weight loss, suggesting that changes in body composition or other factors may override glucagon's acute influence on EE. In contrast, GLP-1RA slows gastric emptying, whereas peristalsis contributes to the DIT; Rodgers et al. [39] observed a decrease in DIT after exenatide treatment. Notably, DIT is only a minor component of TEE, and its variance with GLP-1RA use may not significantly contribute to the changes in glucagon response.

4.5 | EE Assessment and Statistical Analysis

In our review, no studies applied the doubly labeled water method, and only four studies [36, 50] used a 24-h WRIC for TEE assessment. Most studies primarily evaluated RMR for about 20–30 min, followed by RQ estimation. Investigating changes in EE with GLP-1RA mono and combination therapy using gold-standard methods while examining all components of EE warrants further research.

Almost half of the included studies produced inconclusive and potentially inadequate conclusions due to the applied statistical analysis to investigate the effect on EE [39–43, 48, 49, 51, 54–57]. These studies could impact the advancement of the understanding of EE changes with GLP-1RA. For instance, if the RMR of an individual with obesity is simply divided by their body weight, they would seem to have a lower relative RMR when compared to individuals without obesity. However, if FFM is properly considered and not simply as a ratio to RMR, these differences disappear and show that individuals with obesity might not have alterations in EE and even present higher absolute RMR [29, 33]. Additionally, most studies did not determine sample size specifically to detect changes in EE, potentially rendering them underpowered to adequately address this primary research question. Providing guidance on preferred reporting and statistical approaches for EE studies could help standardize approaches and generate valid findings.

4.6 | Future Research

Animal studies have shown potential effects of GLP-1RA and glucagon on remodeling adipose tissue (white adipose tissue to beige/BAT) and increasing BAT thermogenesis [78], lipolysis, and fatty acid oxidation [79], which plays a crucial role in regulating energy metabolism. Oxyntomodulin, a glucagon receptor agonist, also seems to increase BAT thermogenesis; however, to induce BAT thermogenesis, oxyntomodulin may require the activation of GLP-1R [80]. Additionally, glucagon may indirectly increase EE by stimulating the increase in catecholamines (e.g., noradrenaline), cortisol, and fibroblast growth factor-21 concentrations, molecules known to affect EE [66, 80–83]. However, in humans, GLP-1RA effects on EE, especially in white adipose tissue browning and BAT thermogenesis, remain to be further explored and are unclear under thermoneutral conditions [84].

Novel triple agonists combining actions on GLP-1, GIP, and glucagon seem promising for promoting greater weight loss effectiveness [85]. They modulate energy balance by increasing both satiety and EE in animals [86, 87], but future studies evaluating in depth the impact on EE in humans are still warranted. Recommended studies to improve our understanding of the effects of GLP-1RA mono or combination therapy include the application of gold-standard techniques for the assessment of EE (i.e., WRIC or doubly labeled water for free-living assessment) and body composition (i.e., multicomponent model or whole-body magnetic resonance imaging) and application of robust statistical analyses, which would allow for changes in weight and body composition (e.g., FFM and FFM composition) to be included as part of the models.

4.7 | Strengths and Limitations

We conducted a comprehensive systematic literature review across multiple databases and gray literature, guided by an experienced librarian and following PRESS [28] and PRISMA guidelines [27] to ensure quality and transparency. On the other hand, this review has some limitations. We only searched for GLP-1RA monotherapy after 2018 to update a previous systematic review [18]. One reviewer conducted title, abstract, and full-text screening; however, the use of a predesigned screening form, the constant discussion with other authors, and the previous experience with systematic literature searches in the field of pharmacology helped mitigate possible biases. The evidence from this review was derived from a limited number of trials with diverse methodologies, potential issues with statistical power, inconsistent data reporting, and varying adjustments related to EE and data analysis. Lastly, the weight reduction in consequence of incretin-based pharmacology in individuals with obesity and diabetes is less pronounced compared to those with obesity only, which may impact body composition and EE changes. This difference is multifactorial and may include hyperinsulinemia, greater insulin resistance, hyperglucagonemia, background medications, and other factors [88]. However, due to the heterogeneity of the included studies, separate analyses were not feasible.

5 | Conclusion

Limited studies with appropriate statistical methods do not support that acute or chronic GLP-1RA therapy significantly impacts EE independently of weight loss. However, the combination of GLP-1RA with glucagon or GIP may impact EE in different ways, particularly by altering macronutrient oxidation or utilization rates. Notably, most studies have focused solely on RMR, and the interpretation of EE changes in some studies is confounded by concurrent negative energy balance. Further exploration is required of newer drug formulations, dosages indicated for obesity management, gold-standard methods for EE assessment, repeated EE measures over the longer term, and consideration of AT. Understanding the effects of these obesity medications on EE may guide more individualized interventions for different specific obesity phenotypes (e.g., reduced metabolic rate or impaired satiety mechanisms), dose titration for obesity management, and achieve greater treatment responsiveness.

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Conflicts of Interest

The authors declare no conflicts of interest. S.C. is on advisory boards for Novo Nordisk and Bausch Health and has received honoraria from Bausch Health and Obesity Canada. C.M.P. has received honoraria and/or paid consultancy from Abbott Nutrition, Nutricia, Nestle Health Science, Pfizer, Amra Medical, and Novo Nordisk and unrelated funding from Almased for unrelated research. A.M.H. is on advisory boards for Rhythm Pharmaceuticals, Novo Nordisk Canada, and Pfizer Canada and has received honoraria from Soleno Therapeutics; she is a clinical trial investigator for Rhythm Pharmaceuticals, Levo Therapeutics, Acadia Pharmaceuticals, Aardvark Therapeutics, Novo Nordisk, and Eli Lilly.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist. **Table S2:** Last updated literature search strategy performed between October 27 and 28, 2025. Search content: GLP-1 combination therapy.