

Supplementary material

Detailed summary of the impacts of incretin therapies on body weight

Liraglutide

An early study involving Lira investigated body weight changes in 564 middle-aged (46 yr) individuals with obesity ($\text{BMI} = 30\text{--}40 \text{ kg/m}^2$). This 20-week trial revealed that daily Lira doses of 1.2, 1.8, 2.4 and 3.0 mg induced weight loss of 5% (-4.8 kg), 5.6% (-5.5 kg), 6.4% (-6.3 kg), and 7.4% (-7.2 kg), respectively, whereas the placebo group had an average weight loss of 2.9% (2.8 kg) (1). A subsequent trial of daily Lira at 3.0 mg over 2 years in 472 middle-aged (46 yr) individuals with obesity showed that Lira was safe and well tolerated, and induced weight loss of ~8% (-7.8 kg) after the first year, which was sustained during the second year (placebo loss was ~2% or -2 kg) (2). Wadden and colleagues (3) studied body weight maintenance and additional weight loss with Lira after diet-induced weight loss in 422 adults (46 yr) with overweight or obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$ or $\geq 27 \text{ kg/m}^2$ with comorbidities) and reported weight loss of 6.2% (-6 kg) after a 56-week daily Lira dose of 3.0 mg; placebo body weight loss was 0.2% or -0.1 kg. Another study (3.0 mg for 56 weeks in 3731 middle-aged adults, $\text{BMI} \geq 30 \text{ kg/m}^2$ or $\geq 27 \text{ kg/m}^2$ with untreated dyslipidaemia or hypertension) showed body weight reduction of 8% (-8.4 kg) (placebo = 2.7% or -2.8 kg) (4). Similarly, Davies and colleagues (5) used daily doses of 3.0 and 1.8 mg in 846 individuals (55 yr) with type 2 diabetes over a 56-week protocol. In addition to Lira, individuals were encouraged to reduce their energy intake by 500 kcal/d and increase physical activity by ≥ 150 min/week. Individuals taking 3.0 mg reduced body weight by 6% (-6.4 kg), while a dosage of 1.8 mg induced a loss of 4.7% (-5.0 kg). The placebo group showed a modest weight loss of 2% (-2.2 kg). As in the other Lira trials, both treatment and placebo groups received counselling sessions about diet and exercise. The most common side effects associated with Lira administration were mild-to-moderate transient gastrointestinal disorders such as nausea, diarrhea, and vomiting. These

studies of Lira indicate that it is associated with effective, if not impressive, levels of weight reduction relative to placebo.

Semaglutide

A series of trials (the STEP and PIONEER trials) have been conducted to assess the efficacy and safety of Sema administration in individuals with excess weight. The PIONEER trials investigated type 2 diabetes-related outcomes after oral Sema administration at different doses. PIONEER 1 assessed the efficacy and safety of different doses of Sema as monotherapy in 703 patients with type 2 diabetes (HbA1c of 7.0-9.5%) (6). After a 26-week intervention, Sema induced a weight reduction of 2% (-1.7 kg), 2.8 (-2.5 kg), and 4.7% (-4.1 kg) at 3, 7 and 14 mg, respectively, compared to a loss of 1.7% (-1.5 kg) in the placebo group. Sema induced clinically relevant improvement in HbA1c, regardless of the dose (6). Subsequently, PIONEER 2 compared the efficacy and safety of oral Sema administration (14 mg) and empagliflozin (25 mg) in 822 individuals with type 2 diabetes (HbA1c of 7-10.5% on stable metformin) across a 52-week trial. Sema induced body weight reduction of 4.1% (-3.8 kg), while the empagliflozin group had a reduction of 3.9% (-3.6 kg). Sema was associated with a greater HbA1c reduction, compared to empagliflozin (7). Rosenstock and colleagues (8) studied the effects of additional oral Sema versus sitagliptin in 1864 adults with uncontrolled type 2 diabetes (HbA1c of 7.0-10.5% on stable metformin, with or without sulfonylurea). This 26-week trial (PIONEER 3) demonstrated that Sema decreased body weight by 1.3% (-1.2 kg), 2.4% (-2.2 kg), and 3.4% (-3.1 kg) at 3 mg, 7 mg, and 14 mg doses, respectively, while sitagliptin reduced body weight by 0.67% (-0.6 kg). Sema at 7 mg and 14 mg was associated with a greater reduction in HbA1c in comparison with sitagliptin (8).

PIONEER 4 compared the effects of oral Sema versus Lira in 711 individuals with type 2 diabetes (HbA1c of 7-9.5% and stable metformin). This 52-week study revealed that oral Sema (14 mg) induced body weight reduction of 5.4% (-5 kg), whilst Lira (1.8 mg) and placebo induced reductions of 3.2% (-3.1 kg) and 1.3% (-1.2 kg). In addition, Sema was associated with a greater decrease in HbA1c, in comparison with Lira (9). PIONEER 5 studied the efficacy and safety of oral Sema administration (14 mg) in 324 patients (70 yr) with type 2 diabetes and moderate renal impairment (HbA1c of 7.0-9.5%, glomerular filtration rate of 30-59 mL/min per 1.73 m²) (10). After a 26-week trial, the Sema group showed a mean weight loss of 4.1% (-3.7 kg), compared to 1.2% (-1.1 kg) for the placebo group. Furthermore, Sema induced a significant reduction of HbA1c (10). Husain and colleagues reported cardiovascular outcomes associated with oral Sema in PIONEER 6 (11). They randomised 3183 patients with type 2 diabetes to Sema at 14 mg or placebo for a median of 68 weeks. Body weight reductions of 4.6% (-4.2 kg) and 0.8% (-0.8 kg) were evident for Sema and placebo, with no differences in cardiovascular outcomes between groups (11). PIONEER 7 investigated the efficacy and safety of daily oral Sema with doses of 3, 7 or 14 mg versus sitagliptin (100 mg) in 504 individuals (57 yr) with type 2 diabetes (HbA1c of 7.5-9.5%) for 52 weeks (12). They reported a body weight reduction of 3.3% (-2.9 kg) and 0.9% (-0.8 kg) for Sema and placebo, respectively (12). PIONEER 8 subsequently investigated the efficacy, safety, and tolerability of oral Sema or placebo in 731 individuals with type 2 diabetes (HbA1c of 7-9.5%) during a 52-week trial (13). Sema induced body weight reductions of 1.2% (-1 kg), 3.3% (-2.9 kg), and 5.1% (-4.3 kg) at 3, 7 and 14 mg doses, respectively (placebo 0.7% or +0.6 kg) (13). PIONEER 9 studied the dose-response, efficacy, and safety of oral Sema versus Lira (0.9 mg) in 243 Japanese patients with type 2 diabetes (HbA1c of 6.5-9.5%) for 52 weeks and reported decreased body weight of 0.8% (-0.6 kg) and 4.1% (-2.8 kg) for Sema at 7 and 14 mg, respectively (placebo 1.4% or -1 kg) (14). Lira increased body weight by 0.5% (+0.4 kg). Moreover, this study reported a

significant decrease in HbA1c compared with placebo, and Sema demonstrated a safety similar to other GLP-1 agonists (14). The final study from this series (PIONEER 10) investigated oral Sema versus dulaglutide in 458 Japanese individuals with type 2 diabetes (HbA1c of 7.0-10.5%). After the 52-week trial, they reported a body weight reduction of 0.1% (-0.1 kg), 1.7% (-1.2 kg), 3.2% (-2.3 kg), for Sema at 3, 7 and 14 mg, respectively. In contrast, dulaglutide increased body weight by 0.4% (+0.3 kg). Sema was well tolerated and reduced HbA1c (15).

The STEP trials aimed to assess the efficacy and safety of Sema, administered as weekly subcutaneous injections, for the treatment of obesity. STEP 1 assessed the effects of 2.4 mg Sema weekly versus placebo in 1961 adults with overweight or obesity ($\geq 30 \text{ kg/m}^2$ or $\geq 27 \text{ kg/m}^2$ with at least one weight-related comorbidity). Sema reduced body weight by 14.9%, or -15.3 kg, whilst the placebo group showed weight loss of 2.4%, or -2.6 kg (16). STEP 2 compared different doses of Sema (2.4 vs 1.0 mg) and placebo for 68 weeks on body weight in 1210 individuals (55 yr) with excess weight and type 2 diabetes ($\text{BMI} \geq 27 \text{ kg/m}^2$ and HbA1c of 7-10%). Both doses induced significant weight loss of 9.6% (-9.6 kg) and 7.0% (-7.0 kg), versus placebo reduction of 3.4% (-3.4 kg) (17).

STEP 3 investigated the combined effect of Sema (2.4 mg) with an intensive behavioural therapy, which also included an initial 8-week meal replacement diet, on body weight in 611 middle-aged adults (46 yr) with overweight ($\geq 27 \text{ kg/m}^2$ with at least one weight-related comorbidity) or obesity ($\geq 30 \text{ kg/m}^2$) (18). After the 68-week treatment, there was a significant body weight reduction of 16% (-17 kg) in the Sema group, compared to 5.7% (-5.9 kg) for the placebo group. In STEP 4, continued Sema treatment was compared to placebo in middle-aged adults (46 yr) with overweight ($\geq 27 \text{ kg/m}^2$ with at least one weight-related comorbidity) or obesity ($\geq 30 \text{ kg/m}^2$). After an initial 20-week Sema run-in and lifestyle intervention (500-kcal

deficit diet and physical activity recommendation of 150 min/wk), 803 individuals were randomised to Sema at 2.4 mg or placebo for another 48 weeks (19). The run-in period induced a mean body weight loss of 10.6% (-11.1 kg). Thereafter, individuals in the Sema treatment group reported additional weight loss of 7.9% (-7.1 kg) (19). The longer-term effects of Sema treatment were investigated in STEP 5, which assessed the 2-year effects of Sema (2.4 mg) in 304 middle-aged adults with overweight (≥ 27 kg/m² with at least one weight-related comorbidity) or obesity (≥ 30 kg/m²) (20). Both groups received a lifestyle intervention of 500-kcal deficit diet and physical activity counselling. After 104 weeks, Sema induced a significant mean weight loss of 15.2% (-16.1 kg), while the placebo group reduced weight by 2.6% (-3.2 kg). This study also demonstrated a positive effect of Sema on cardiometabolic risk factors such as waist circumference, blood pressure, and HbA1c (20).

Given the known phenotypic differences between Asian and non-Asian populations in terms of obesity and body composition, STEP 6 investigated the effects of Sema in 401 middle-aged adults from Japan and South Korea with overweight (≥ 27 kg/m² with at least one weight-related comorbidity) or obesity (≥ 30 kg/m²), with or without type 2 diabetes, and who had experienced at least one unsuccessful diet-based intervention to lose weight (21). At week 68, Sema at 2.4 mg and 1.7 mg induced body weight reductions of 13.2% (-11.5 kg) and 9.6% (-8.3 kg), respectively, whilst the placebo group lost an average of 2.1% (-1.9 kg). In addition, Sema promoted significant reductions in abdominal visceral fat (21). Rubino and colleagues (22) compared the efficacy of weekly Sema (2.4 mg) vs daily Lira (3.0 mg) in 338 individuals with overweight (≥ 27 kg/m² with at least one weight-related comorbidity) or obesity (≥ 30 kg/m²) in a 68-week randomised controlled trial (STEP 8). Although both drugs promoted reductions in body weight, Sema induced a body weight reduction of 15.8% (-16.2 kg), compared to Lira 6.4% (-6.6 kg). The pooled placebo group showed a body weight reduction of 1.9% (-2.1 kg).

A lifestyle intervention (diet- and exercise-based counselling intervention) was undertaken alongside the pharmacological treatments (22). Mild-to-moderate transient gastrointestinal events have been also reported after Sema use, being nausea and constipation the most common.

Tirzepatide

Tz is a recent incretin hormone therapy developed for obesity treatment and management. In contrast to other drugs mentioned above, it acts as a dual agonist for both GIP and GLP-1 receptors, so is referred to as a “twincretin” (23). Initial studies (the SURPASS trials) assessed the efficacy of Tz, administered as a weekly subcutaneous injection, for the treatment of type 2 diabetes. SURPASS 1 assessed Tz administration in 478 patients with type 2 diabetes (HbA1c 7.0% to 9.5%) and BMI of 23 kg/m² or higher) during a 40-week Tz treatment at 5, 10, and 15 mg. These Tz doses induced weight loss of 7.9% (-7 kg), 9.3% (-7.8 kg), and 11% (-9.5 kg), respectively (placebo 1% or -0.7 kg). This study also reported a reduction in HbA1c following Tz treatment with no increase in hypoglycaemia risk, and mild-to-moderate side effects (e.g., nausea, diarrhoea, vomiting) (24). SURPASS 2 compared the efficacy and safety of Tz (5, 10, or 15 mg) and Sema (1 mg) in 1879 individuals with type 2 diabetes (HbA1c 7-10.5% and BMI at least 25 kg/m²) across a 40-week trial. Weight losses of 8.5% (-7.8 kg), 11% (-10.3 kg), and 13.1% (-12.4 kg) were reported for Tz at 5, 10 and 15 mg doses, while Sema reduced weight by 6.7% (-6.2 kg). Tz was also superior to Sema in reducing HbA1c levels.(25) Ludvik and colleagues (26) (SURPASS 3) studied the effects of weekly Tz (5, 10 and 15 mg) versus daily administration of insulin degludec as an add-on to metformin in 1444 individuals with type 2 diabetes (HbA1c 7-10.5%, stable metformin treatment and BMI of at least 25 kg/m²). After the 52-weeks of treatment, Tz at 5, 10 and 15 mg induced weight reductions of 8% (-7.5 kg), 11.3% (-10.7 kg) and 13.6% (-12.9 kg), respectively, whilst the insulin degludec increased weight by

2.4% (-2.3 kg). Tz was superior for the reduction of HbA1c levels, with lower risks of hypoglycaemia in comparison with insulin degludec (26). SURPASS 4 focused on the cardiovascular safety of Tz when assessing the efficacy and safety of weekly Tz administration and glargine (100 U/mL) treatment in 2002 individuals with type 2 diabetes (T2D) and increased cardiovascular risk (HbA1c of 7.5-20.5%, BMI of at least 25 kg/m² and increased risk of cardiovascular events) (27). After the 52-week intervention, the Tz groups had reduced weight by 7.9% (-7.1 kg), 10.5% (-9.5 kg), and 13% (-11.7kg), in response to 5, 10 and 15 mg doses respectively, whereas glargine treatment was associated with an increase in body weight of 2.1% (+1.9 kg). Tz demonstrated superior HbA1c reduction and a lower hypoglycaemia risk, with no apparent increase in cardiovascular risk compared to glargine (27).

SURPASS 5 studied Tz added to insulin glargine in 475 individuals with T2D and inadequate glycaemic control (HbA1c 7.0-10.5%, BMI \geq 23 kg/m², on stable doses of insulin glargine >20 IU/d or >0.25 IU/kg/d), with or without metformin (\geq 1500 mg/d) (28). Body weight reductions of 5.6% (-5.4 kg), 7.9% (-7.5 kg), and 9.1% (-8.8 kg) occurred after 40 weeks of Tz administration at 5, 10 and 15mg. The placebo group showed an increase in body weight of 1.7% (+1.6 kg). This study also reported significant improvements in glycaemic control when Tz was added to insulin glargine (28).

Given the significant weight loss found in trials assessing the efficacy of Tz for the treatment of T2D, Tz was investigated for the treatment of obesity *per se*. A recently published trial (SURMOUNT-1) showed that weekly Tz administration over a 72-week period in 2539 individuals with obesity, induced a body weight loss of 15% (-15.4 kg) at a dose of 5 mg, 19.5% (-20.6 kg) at 10 mg, and 20.9% (-22.1 kg) at 15 mg (29). The placebo group had a mean body weight change of 3.1% (-3.2 kg) (29). In addition, SURMOUNT-2 used weekly

subcutaneous Tz administration (10 and 15 mg) for 72 weeks in 938 individuals with obesity and T2D, and reported significant weight loss of 13.4% and 15.7%, respectively, while the placebo group presented a weight loss of 3.3% (30). Less weight loss in SURMOUNT-2 in comparison to SURMOUNT-1 is consistent with these patients having T2D in addition to obesity. The side effects reported for Tz were mild-to-moderate gastrointestinal events with nausea, vomiting and diarrhea as the most common.

Retatrutide

Reta is the most recent incretin hormone studied for obesity treatment and management. It is the first of its class that acts as a triple-incretin, being an agonist for GLP-1, GIP, and glucagon receptors GLP-1, GIP, and glucagon receptors (31). An introductory study has investigated the effect of 24- and 48-week Reta therapy on body weight in 338 middle-aged individuals (48 yr) with overweight or obesity (i.e. BMI ranging from 27 to 29.9 kg/m² with at least one weight-related comorbidity or BMI from 30 to 50 kg/m², respectively). After 24 weeks of weekly Reta administration, Reta induced a weight loss of 7.2% (-7.7 kg) at 1 mg dose, 11.8% (-12.7 kg) at 4 mg dose with an initial dose of 2 mg, 13.9% (-14.9 kg) at 4 mg dose with an initial dose of 4 mg, 16.7% (-17.8 kg) at 8 mg with an initial dose of 2 mg, 17.9% (-19.4 kg) at 8 mg with an initial dose of 4 mg, and 17.5% (-18.9 kg) at 12 mg with an initial dose of 2 mg. The placebo group achieved a modest weight loss of 1.6% (-1.7 kg). After 48 weeks, Reta therapy induced a body weight reduction of 8.7% (-8 kg) at 1 mg dose, 16.3% (-17.5 kg) at 4 mg dose with an initial dose of 2 mg, 17.8% (-18.4 kg) at 4 mg dose with an initial dose of 4 mg, 21.7% (-22.3 kg) at 8 mg with an initial dose of 2 mg, 23.9% (-26.7 kg) at 8 mg dose with an initial dose of 4 mg, 24.2% (-26.4 kg) at 12 mg dose with an initial dose of 2 mg. The placebo group achieved a mean weight loss of 2.1% (-3.3 kg) (32).

Another study investigated the effect of weekly Reta administration at different doses on 281 middle-aged individuals with type 2 diabetes (HbA_{1c} of 7 – 10.5% or 53 – 91.3 mmol/mol and BMI of 25 – 50 kg/m²) using 24 and 36 weeks as endpoints. After 24 weeks, they reported a weight loss of 2.4% (-2.36 kg) at 0.5 mg Reta dose, 5.6% (-6.11 kg) at 4 mg with initial Reta dose of 2 mg, 9.3% (-8.64 kg) at 4 mg Reta dose, 12.6% (-12.37 kg) at 8 mg with initial Reta dose of 2 mg, 14.5% (-13.95 kg) at 8 mg with initial Reta dose of 4 mg, and 13% (-13.03 kg) at 12 mg Reta dose. Placebo recipients experienced a weight reduction of 2.1% (-1.97 kg), while Dulaglutide at 1.5 mg dose reduced body weight by 1.3% (-1.27 kg) (33). After 36 weeks of treatment, Reta induced a weight loss of 3.2% (-3.3 kg) at 0.5 mg, 7.9% (-7.3 kg) at 4 mg with initial dose of 2 mg, 10.4% (-10.4 kg) at 4 mg, 16.8% (-16.5 kg) at 8 mg with initial dose of 2 mg, 16.3% (-16.1 kg) at 8 mg with initial dose of 4 mg, and 16.9% (-17.2 kg) at 12 mg. Dulaglutide 1.5 mg and placebo resulted in weight loss of 2% (-2 kg) and 3% (-3.3 kg), respectively (33). In addition, Urva and colleagues (34) investigated the effect of different doses of weekly Reta treatment in 72 individuals with type 2 diabetes over a 12-week period. Inclusion criteria included type 2 diabetes diagnosis of at least 3 months, HbA_{1c} value of 7 – 10.5%, BMI of 23 – 50 kg/m², and stable body weight (<5% weight change 3 months prior to the beginning of the treatment). Weight loss of 2.5% (-2.1 kg) at Reta 1.5 mg, 5.2% (-4.4 kg) at Reta 3 mg dose, 8.1% (-7.5 kg) at Reta 6 mg dose with initial dose of 3 mg, and 10.2% (-8.6 kg) at Reta 12 mg dose. Increases in body weight of 0.5% (+0.4 kg) and 0.4% (+0.3 kg) were observed for Dulaglutide 1.5 mg dose and placebo, respectively. Mild-to moderate gastrointestinal events including nausea, diarrhea, vomiting, and constipation were reported after Reta utilization.

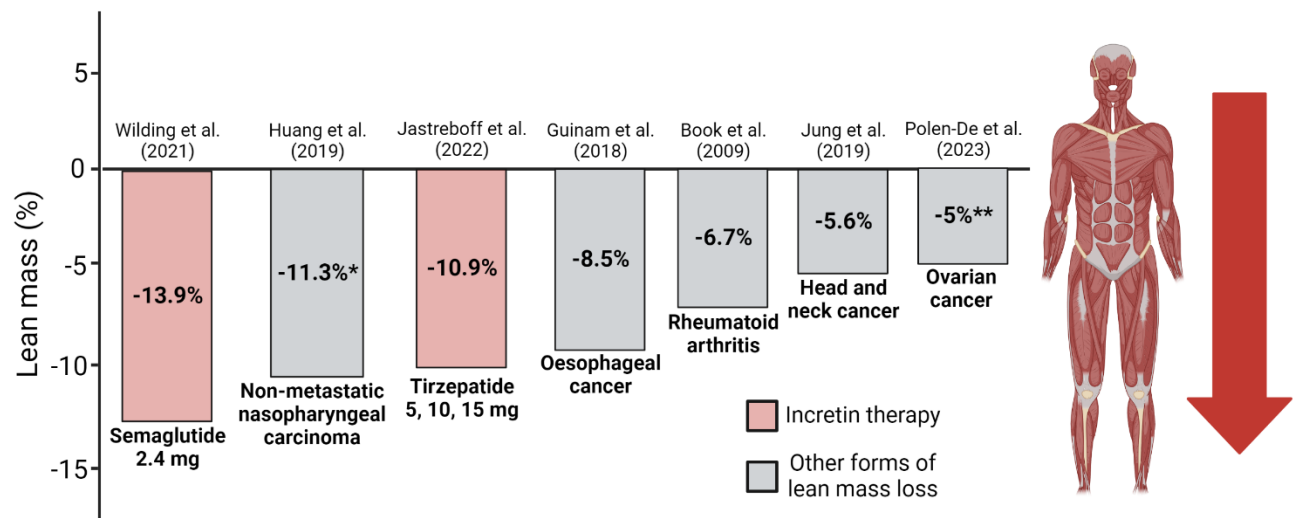
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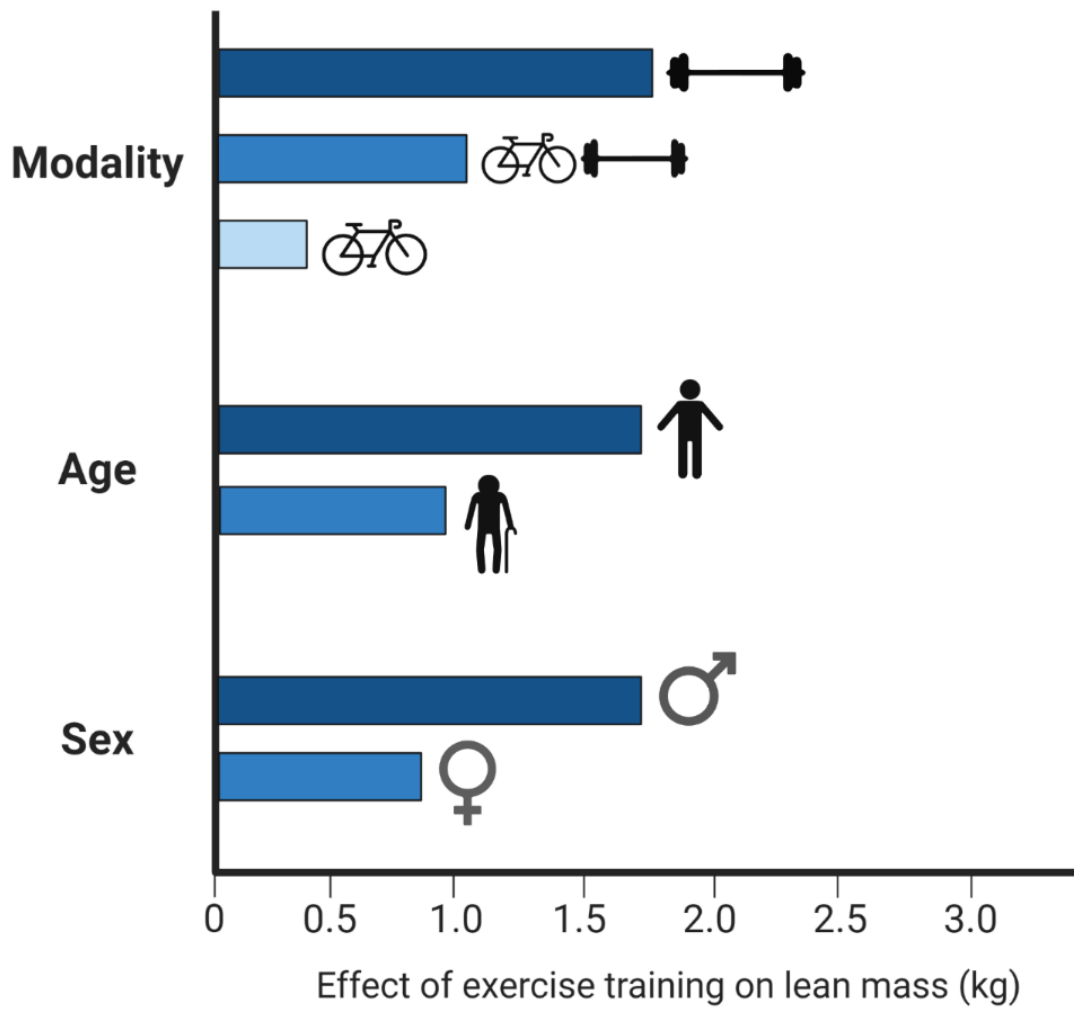
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Supplementary Figure 1. Incretin therapy-based loss of lean mass and its comparison with other forms of lean mass loss. The loss of lean mass induced by incretin therapies is similar in magnitude to some major diseases. *Data presented regarding decrease in muscle area assessed by computed tomography; **Data presented regarding decrease in skeletal muscle index assessed by computed tomography.



Supplementary Figure 2. Moderators of the impact of exercise training on lean mass.