PERSPECTIVES IN CARE

Incretin-Based Weight Loss Pharmacotherapy: Can Resistance Exercise Optimize Changes in Body Composition?

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This narrative review highlights the degree to which new antiobesity medications based on gut-derived nutrient-stimulated hormones (incretins) cause loss of lean mass, and the importance of resistance exercise to preserve muscle. Glucagon-like peptide 1 receptor agonists (GLP-1RA) induce substantial weight loss in randomized trials, effects that may be enhanced in combination with glucose-dependent insulinotropic polypeptide (GIP) receptor agonists. Liraglutide and semaglutide (GLP-1RA), tirzepatide (GLP-1 and GIP receptor dual agonist), and retatrutide (GLP-1, GIP, and glucagon receptor triple agonist) are peptides with incretin agonist activity that induce ∼15–24% weight loss in adults with overweight and obesity, alongside beneficial impacts on blood pressure, cholesterol, blood glucose, and insulin. However, these agents also cause rapid and significant loss of lean mass (∼10% or ∼6 kg), comparable to a decade or more of aging. Maintaining muscle mass and function as humans age is crucial to avoiding sarcopenia and frailty, which are strongly linked to morbidity and mortality. Studies indicate that supervised resistance exercise training interventions with a duration >10 weeks can elicit large increases in lean mass (∼3 kg) and strength (∼25%) in men and women. After a low-calorie diet, combining aerobic exercise with liraglutide improved weight loss maintenance compared with either alone. Retaining lean mass during incretin therapy could blunt body weight (and fat) regain on cessation of weight loss pharmacotherapy. We propose that tailored resistance exercise training be recommended as an adjunct to incretin therapy to optimize changes in body composition by preserving lean mass while achieving fat loss.

Obesity reduces life expectancy and contributes to the development of our most prevalent and costly chronic diseases, including hypertension, type 2 diabetes, coronary artery disease, stroke, nonalcoholic fatty liver disease, and chronic kidney disease. Typically defined by reference to indices of gross body weight (e.g., BMI >30 kg/m^2), obesity-related health risk is primarily attributable to excess body fat and is strongly associated with physical inactivity. There has never been a more overweight or sedentary population than 21st century Western society. The global prevalence of obesity will soon reach 18% in men and 21% in women (1), and it has doubled since the 1980s (2). Approximately 604 million people had a BMI >30 kg/m^2 in 2015, and it is estimated that 1 billion people will have obesity by the year 2030 (3). Cardiovascular diseases account for ∼70% of all deaths ascribed to excess body weight (4), and slowing the increase in obesity by 5% could reduce its associated costs by $3.3 billion annually between 2020 and 2060 (5).

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Given the substantial health and economic burden of obesity and its associated comorbidities, effective treatment is a major public health priority (6). Losing 5–10% of body weight reduces lipids (~20% triglycerides, ~15% LDL cholesterol) (7), blood pressure (~5/4 mmHg) (8), and glycated hemoglobin (8) and improves insulin sensitivity (9). Broadly, weight loss interventions are categorized as dietary, exercise based, pharmacological, surgical, or a combination of these. Each approach possesses limitations. Dietary and exercise interventions are difficult to sustain; around 50% weight regain occurs within a year of stopping dietary interventions, which reverses the health benefits (10). Other currently approved antiobesity medications (e.g., phentermine, orlistat, bupropion-naltrexone, and the combination of phentermine and topiramate) typically lead to smaller amounts of weight loss than the new incretin-based therapies (11). Surgical interventions can induce considerable short-term weight loss, and extended follow-up of bariatric surgery cohorts suggests reductions in longer-term cardiovascular risk (12). Newer procedures have fewer complications, but few eligible adults choose to pursue bariatric surgery.

The use of endogenous nutrient-stimulated hormones released from the gut (incretins) increasingly represents a novel strategy for the medical management of obesity. Incretins are intestinal hormones secreted in response to nutrient entry into the gut that induce insulin secretion and inhibit glucagon release. This response is impaired in obesity (13). Glucagon-like peptide-1 receptor agonists (GLP-1RA) improve glycemic control (13), slow gastric emptying, and reduce appetite and food intake. Animal studies indicate that they also impact neural centers responsible for hedonic and appetite control (14). Glucose-dependent insulinotropic polypeptide (GIP) receptor agonists may regulate energy balance in the brain and adipose tissue (15). These agents represent a new and effective treatment option for obesity, highlighting the need to better understand how to optimize health during and following rapid weight loss.

IMPACT OF INCRETIN THERAPY ON BODY WEIGHT

Several randomized placebo-controlled trials have been conducted using incretin mimetic hormones to investigate their efficacy and safety for the treatment of type 2 diabetes and/or obesity management (Fig. 1). Liraglutide (Lira), the first GLP-1RA approved for obesity, induced weight loss of ~8% (−8.4 kg) vs. 2.6% (−2.8 kg) in the placebo group in a trial conducted on 3,731 patients with overweight or obesity (16) (see the Supplementary Material and references therein). In that study, all participants received counseling on lifestyle modification. A subsequent 68-week intervention in middle-aged adults with overweight or obesity using semaglutide (Sema) (2.4 mg) reduced body weight by 14.9% (−15.3 kg) versus 2.4% (−2.6 kg) in the placebo group (17). Moreover, recent evidence demonstrated that a weekly dose of Sema (2.4 mg) reduced the risk of major adverse cardiovascular events by 20% in adults with overweight and obesity without diabetes over a mean duration of follow-up of 40 months (18) (for details on additional studies, see the Supplementary Material and references therein). The most common side effects of GLP-1RA are nausea, diarrhea, and vomiting. In a 68-week comparison of Sema 2.4 mg weekly versus once-daily Lira 3.0 mg in adults with obesity, all of whom received counseling to achieve a 500 kcal/day energy deficit and meet physical activity recommendations (≥150 min/week), the mean weight change from baseline was –15.8% with Sema versus –6.4% with Lira (19).

Tirzepatide (Tz), a dual incretin that acts as both a GLP-1RA and GIP receptor agonist, had even larger effects on weight loss (−20.9%, or −22.1 kg, after a 72-week intervention vs. 3.1%, or −3.2 kg, placebo) in middle-aged adults with obesity or overweight and at least one weight-related complication (20). In a study of adults with obesity and type 2 diabetes, 15.7% weight loss was reported after 72 weeks (21) (see the Supplementary Material regarding impacts of incretins). Treatment regimens involve gradual uptitration of Tz doses. Mild to moderate gastrointestinal side effects, such as nausea, vomiting, and diarrhea, were the most common.

Recently, a new study tested the effects of retatrutide, a triple incretin that is an agonist of GIP, GLP-1, and glucagon receptors, on body weight in middle-aged individuals with overweight and obesity (22). That study reported a weight loss of 24.2% (−26.4 kg) of total body weight, with the highest dose administered (12 mg) after 48 weeks of treatment (vs. −2.1% with placebo) (22) (see the Supplementary Material). Mild to moderate gastrointestinal events, including nausea, diarrhea, vomiting, and constipation, were reported.

Thus, incretin-based weight loss pharmacotherapy achieves ~15–24% reductions in body weight. Sema, Tz, and retatrutide are given as weekly subcutaneous injections. Other formulations, such as the combination of Sema with the long-acting agonist amylin analog cagrilintide (23) and oral formulations such as orforglipron (24), are outside the scope of this review.

IMPACT OF INCRETIN THERAPY ON FAT AND LEAN MASS

An important but often overlooked factor in incretin studies relates to the type of weight lost. Maintaining muscle mass (25) and function (26,27) is crucial to avoiding sarcopenia and frailty, which are strongly linked to morbidity and mortality as humans age (28,29). Large randomized controlled trials typically have not presented changes in body composition or impacts on lean mass (LM). The studies that have addressed body composition have reported distinct outcomes, including those related to skeletal muscle mass, fat-free mass, and LM. While MRI and computed tomography are considered gold standards for skeletal muscle mass assessment, these methods are expensive and time-intensive, and widespread application is unfeasible. LM, which incorporates skeletal muscle mass as its major component, is measured by dual-energy X-ray absorptiometry (DXA), a relatively fast, inexpensive, and accessible approach that nonetheless possesses high precision and reproducibility for the assessment of LM (30).

Studies that have reported the effects of incretin therapies on body composition, and their potential impact on LM, are summarized in Table 1. Briefly, Astrup et al. (31) assessed changes in body composition via DXA after 20-week Lira administration at different doses (1.2, 1.8, 2.4, and 3.0 mg) in 72 individuals with obesity (BMI 30–40 kg/m^2). They found fat mass losses of 13.9% (−6 kg), 13% (−5.9 kg), 16.5% (−7 kg), and 15.4% (−6.8 kg), respectively. Lira also induced LM losses of 0.9% (−0.5 kg), 2.9% (−1.5 kg), 2.6% (−1.3 kg), and 2% (−1.1 kg). Interestingly, the placebo group showed a notable fat mass loss of 11.8% (−5.4 kg) and LM loss of 1.3% (−0.7 kg) (31). Corroborating these findings, a clinical trial in 44

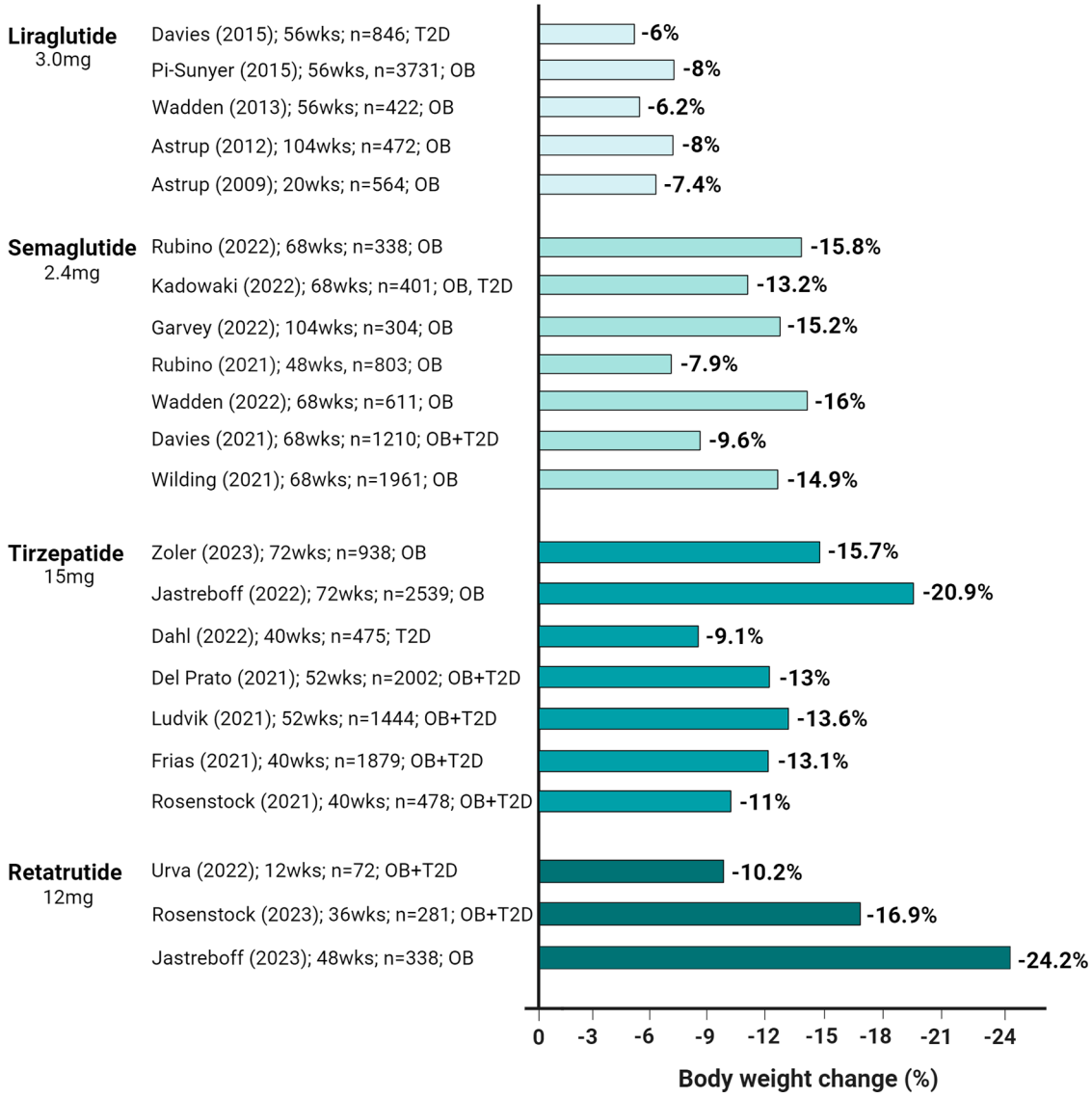

Figure 1—Impact of Lira, Sema, Tz, and retatrutide on body weight in randomized controlled trials. OB, obesity; T2D, type 2 diabetes.

individuals with type 1 diabetes and overweight or obesity revealed a fat mass loss of 14.1% (−4.6 kg) after a 26-week Lira (1.8 mg) treatment and a significant LM loss of 4.7% (−2.5 kg) (32). Another study investigated changes on body composition after Lira administration (3.0 mg) in 28 individuals with excess weight and type 2 diabetes across 24 weeks and reported a fat mass loss of 5.6% (−2 kg) and LM loss of 0.7% (−0.39 kg) (33).

Body composition has also been assessed via DXA in response to Sema administration in 140 individuals with overweight and obesity who underwent 68 weeks of therapy at 2.4 mg/week. In the context of a body weight reduction of 14.9% (−15.3 kg) and fat reduction of 24.7% (−10.4 kg), individuals also lost an average of 13.9% of their total LM (−6.9 kg) (17). Similarly, Jastreboff et al. (20) showed in 160 individuals who underwent DXA assessment that weekly administration of Tz across a 72-week period in middle-aged adults (45 years) with obesity resulted in a total fat mass loss of 33.9% (17 kg) (Fig. 2). Despite an increase of 7.4% in the percentage of LM (due to the proportionately greater loss of fat mass) (Fig. 3), there was an absolute decrease in LM of 6 kg (Fig. 3). That study used a 20-week dose escalation period and three sequential doses of Tz (5, 10, and 15 mg), and the average of all three doses for body composition outcomes was reported (20). The loss of 6 kg LM likely underestimates the loss of LM at higher doses of Tz and in more responsive individuals. This is a profound level of muscle loss (34). It is possible that the loss of LM parallels the loss of fat and reduction in overall weight, reflecting the dosage and reaching a plateau after extended durations of treatment. It is not known whether a slower dose titration of these medications to bring about slower weight loss would cause less loss of LM.

WHY MUSCLE MASS MATTERS

The development of obesity is affected by the quantity and quality of muscle mass and its metabolic rate; individuals with obesity possess lower levels of muscular strength than normal-weight counterparts when strength is adjusted for body mass (35). Obesity also contributes to an increase in intramuscular fat, which in turn decreases muscle quality (36). While the relationship between obesity and reduced muscle mass and strength is more pronounced in the elderly (37), evidence

Table 1—Effects of incretin therapies on body composition

Reference and medication	Study population (*N*, health condition, age)	Intervention duration (weeks)	Change in body weight (kg/%)	Change in fat mass (kg/%)	Change in LM (kg/%)
Astrup et al. (2012) (31)	564 (change in body weight) or 84 (change in fat mass or LM) individuals with OB, 46 ± 10 years	52 (change in body weight) or 20 (change in fat mass or LM)			
Lira 1.2 mg			−3.8 (−4)	−6.0 (−13.9)	−0.5 (−0.9)
Lira 1.8 mg			−5.4 (−5.5)	−5.9 (−13)	−1.5 (−2.9)
Lira 2.4 mg			−6.1 (−6.2)	−7.0 (−16.5)	−1.3 (−2.6)
Lira 3.0 mg			−7.8 (−8)	−6.8 (−15.4)	−1.1 (−2.0)
Orlistat			−3.9 (−4.1)	−5.5 (−13.3)	0.4 (0.9)
Placebo			−2.0 (−2.1)	−5.5 (−11.9)	−0.7 (−1.3)
Rondanelli et al. (2016) (33)	28 individuals with OB and T2D, 59 ± 9 years	24			
Lira 3.0 mg			−2.5 (−2.6)	−2 (−5.6)	−0.4 (−0.7)
Schmidt et al. (2022) (32)	44 individuals with overweight/OB and T1D, 50 ± 14 years	26			
Lira 1.8 mg			−7 (−8.1)	−4.6 (−14.1)	−2.5 (−4.7)
Placebo			−0.3 (−0.3)	−0.3 (−0.9)	0 (0)
Lundgren et al. (2021) (77)	195 individuals with OB, 42 ± 12 years	52			
Lira 3.0 mg			−0.7 (−0.7)	−2 (−5.3)	0
Lira 3.0 mg + exercise			−3.4 (−3.5)	−4.7 (−12.1)	0.5 (0.8)
Exercise			2 (−2.1)	−1.4 (−3.8)	2.1 (3.4)
Placebo			6.1 (6.3)	2.6 (7)	2.9 (4.7)
Frøssing et al. (2018) (89)	72 women with PCOS and overweight/OB, 31 ± 6 years	26			
Lira 1.8 mg			−5.2 (−5.5)	−2.6 (−7.2)	−2.4 (−4.1)
Placebo			0.2 (0.2)	0.3 (0.8)	0.1 (0.2)
Harder et al. (2004) (90)	33 individuals with T2D, 60 ± 10 years	8			
Lira 0.6 mg			−2.1 (−2)	−1.6 (−3.9)	0.6 (1)
Placebo			−2 (−2)	−0.7 (−1.8)	−0.2 (−0.4)
Jendle et al. (2009) (91), LEAD-2	160 individuals with OB and T2D, 57 ± 9 years	26			
Lira 0.6 mg			−0.9 (−1)	−0.7 (−0.5)	−0.3‡
Lira 1.2 mg			−2 (−2.3)	−1.6 (−1.1)	−0.8‡
Lira 1.8 mg			−3.2 (−3.6)	−2.4 (−1.2)	−1.5‡
Glimepiride			1.7 (1.9)	1.1 (0.4)	1.3‡
Placebo			−1.3 (−1.4)	−1.1 (−0.2)	−1.3‡
Jendle et al. (2009) (91), LEAD-3	61 individuals with OB and T2D, 53 ± 11 years	52			
Lira 1.2 mg			−2.4 (2.6)	−2 (−0.9)	−1.1
Lira 1.8 mg			−2.3 (−2.5)	−1 (−0.3)	−1.5
Glimepiride			2 (2.2)	2.4 (2.6)	−0.6
Li et al. (2014) (92)	31 individuals with OB and T2D, 49 ± 11 years	12			
Lira 1.2 mg			−5.1 (−5.6)	−3.8 (−11.2)	−1.5 (2.8)
Perna et al. (2016) (93)	9 individuals with OB and T2D, 68 ± 4 years	24			
Lira 3.0 mg			−2.0 (−2.3)	−1.5 (−4.9)	0.1 (0.2)
Feng et al. (2019) (94)	85 individuals with T2D and NAFLD, 47 ± 2 years	24			
Lira 1.8 mg			−5.6 (−7)	−3.6 (−14.3)	−0.2 (−0.4)
Metformin			−3.6 (−4.8)	−2.7 (−11.6)	0.1 (0.2)
Gliclazide			−0.6 (−0.8)	−0.6 (2.4)	−0.8 (−1.6)
Volpe et al. (2022) (95)*	40 individuals with T2D, 65 ± 11 years	26			
Sema 1.0 mg			−9.9 (−9.5)	−3 (−17.8)	−1.5 (−5.4)
Blundell et al. (2017) (96)†	30 individuals with OB, 42 ± 20 years	12			
Sema 1.0 mg			−5 (−4.9)	−3.5‡	−1.1‡
Placebo			1 (1)	0.3‡	0.5‡
Wilding et al. (2021) (17)	140 individuals with overweight/OB, 46 ± 13 years	68			
Sema 2.4 mg			−15.3 (−14.9)	−10.4 (−24.7)	−6.9 (13.9)
Placebo			−2.6 (−2.4)	−1.17 (−2.9)	−1.5 (−2.9)

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Table 1—Continued

Reference and medication	Study population (*N*, health condition, age)	Intervention duration (weeks)	Change in body weight (kg/%)	Change in fat mass (kg/%)	Change in LM (kg/%)
Jastreboff et al. (2022) (20)	2,539 individuals with OB,	72			
Tz 5.0 mg	47 ± 13 years		−15.4 (−15)		
Tz 10.0 mg			−20.6 (−19.5)	−17 (−33.9)#	−6 (−10.9)#
Tz 15.0 mg			−22.1 (−20.9)		
Placebo			−3.2 (−3.1)	−4.2 (−8.2)	1.4 (−2.6)

LEAD-2, Liraglutide Effect and Action in Diabetes-2; LEAD-3, Liraglutide Effect and Action in Diabetes-3; NAFLD, nonalcoholic fatty liver disease; OB, obesity; PCOS, polycystic ovary syndrome; T1D, type 1 diabetes; T2D, type 2 diabetes. *Used a phase-sensitive bioimpedance analyzer for body composition assessment. †Used air displacement plethysmography for body composition assessment. ‡Did not provide enough data for the calculation of percentage changes. #Combined doses.

indicates that excess adipose tissue impairs muscle recruitment and activation, even in young individuals (38). Resting energy expenditure is responsible for the largest component of total energy expenditure, and expenditure related to muscle metabolism (i.e., synthesis and breakdown of muscle protein) is a major determinant of basal metabolic rate (39), which can vary significantly depending on the volume and quality of muscle mass; a 100 kcal/day difference in energy expenditure represents a difference of approximately 4.7 kg fat mass across a year (40). This emphasizes the critical importance of preserving muscle mass for the maintenance of optimal body composition with age (41).

Progressive age-related deterioration in muscle mass and strength, termed sarcopenia, is associated with adverse consequences for health and physical function (25). Loss of muscle mass can initiate a state of frailty that is linked to falls in the elderly. Falls have significant impacts on health care budgets, accounting for $50 billion in U.S. in 2015 (42). Moreover, loss of muscle is associated with increased risk of cardiovascular disease and death (43). Elderly individuals classified as having low strength have a 50% higher likelihood of death from all-cause mortality compared with those with normal strength at the same age (44). Recent evidence indicates that individuals in the lowest muscle mass tertile had an 81% higher risk of cardiovascular events compared with those in the highest muscle mass tertile (45), and loss of muscle mass is estimated to increase the risk of cardiovascular and all-cause mortality by 35% (46).

That the loss of LM and muscle mass is important in the context of obesity management is highlighted by an analysis of the impacts of bariatric surgery (47), which indicated that the ∼8-kg loss in LM (reflecting 21% of the total weight lost) may have long-term implications for functional capacity, resting energy expenditure, bone strength, metabolic health, the drive to eat, and weight regain. The increased risk of sarcopenia and strength loss emphasizes the potential for inducing sarcopenic obesity, where the detrimental effects of low muscle mass and high fat mass may potentiate each other (47). Nonetheless, it should be acknowledged that while greater incretin-induced body weight reduction induces larger improvements in HbA_{1c}, triglycerides, ALT, waist circumference, and blood pressure (48), it remains unclear whether loss in LM has detrimental long-term impacts on cardiovascular risk factors.

IMPACT OF INCRETIN THERAPIES COMPARED WITH OTHER FORMS OF MUSCLE LOSS

As discussed above, Sema administration is associated with an LM loss of 13.9% (∼6.9 kg) over a period of 68 weeks (17), while Tz induced a 10.9% (6 kg) loss over 72 weeks of therapy (20). For context, after chemoradiotherapy for nonmetastatic nasopharyngeal carcinoma, patients experienced a loss of 11.3% in muscle area (49), while patients under neoadjuvant therapy for esophageal cancer showed an LM loss of 8.5% (50). In addition, a decrease of 5.6% in LM was observed in patients with advanced-stage head and neck cancer (51), and patients with advanced ovarian cancer presented a decrease in skeletal muscle index of 5% (Supplementary Fig. 1) (52). These comparisons highlight the potential clinical significance of the levels of LM loss associated with incretin therapies, with losses also comparable to the long-term effects of aging; it can be estimated that loss of 6 kg LM associated with incretin therapies approximates the impact of a decade or more of human ageing on skeletal muscle mass (34,53). Strategies aiming to preserve LM are needed to prevent the significant LM loss associated with incretin-based therapies.

IMPACT OF EXERCISE TRAINING ON LM

Weight loss, either intentional via diet and exercise or unintentionally when associated with disease, is accompanied by a loss in skeletal muscle mass that can amount to up to ∼40% of total weight loss (54). Exercise training has the potential to increase muscle mass, thus preventing or mitigating adverse effects of weight loss interventions. Several factors modulate the impact of exercise on body composition during weight loss (Supplementary Fig. 2).

Impact of Exercise Modality

The American College of Sports Medicine (ACSM) endorses resistance training (RT) over other exercise modalities for gain or preservation of muscle mass (55). In healthy untrained men (n = 38, age 37 ± 7 years), the cross-sectional area of the quadriceps femoris increased by 6% after 21 weeks of RT, while endurance training (ET) (e.g., cycling) induced a modest increase of 2% (56). In addition, a randomized crossover study in younger adults (25 ± 5 years), involving 3 months of ET and RT, reported a significant increase in LM that was larger in response to RT than ET (ET Δ0.4 ± 1.1 kg vs. RT Δ1.2 ± 1.1 kg) (57). In this crossover trial, a larger proportion of individuals responded with an increase in LM as a result of RT (84%) than ET (58%) (57).

A study involving 119 sedentary adults with overweight and obesity (49.7 ± 10.3 years) indicated that 8 months of RT (+1.09 kg) and combined RT/ET (+0.81 kg), but not ET alone (−0.10 kg), increased LM (58). Another trial of 12 weeks of RT and ET on body composition in 27

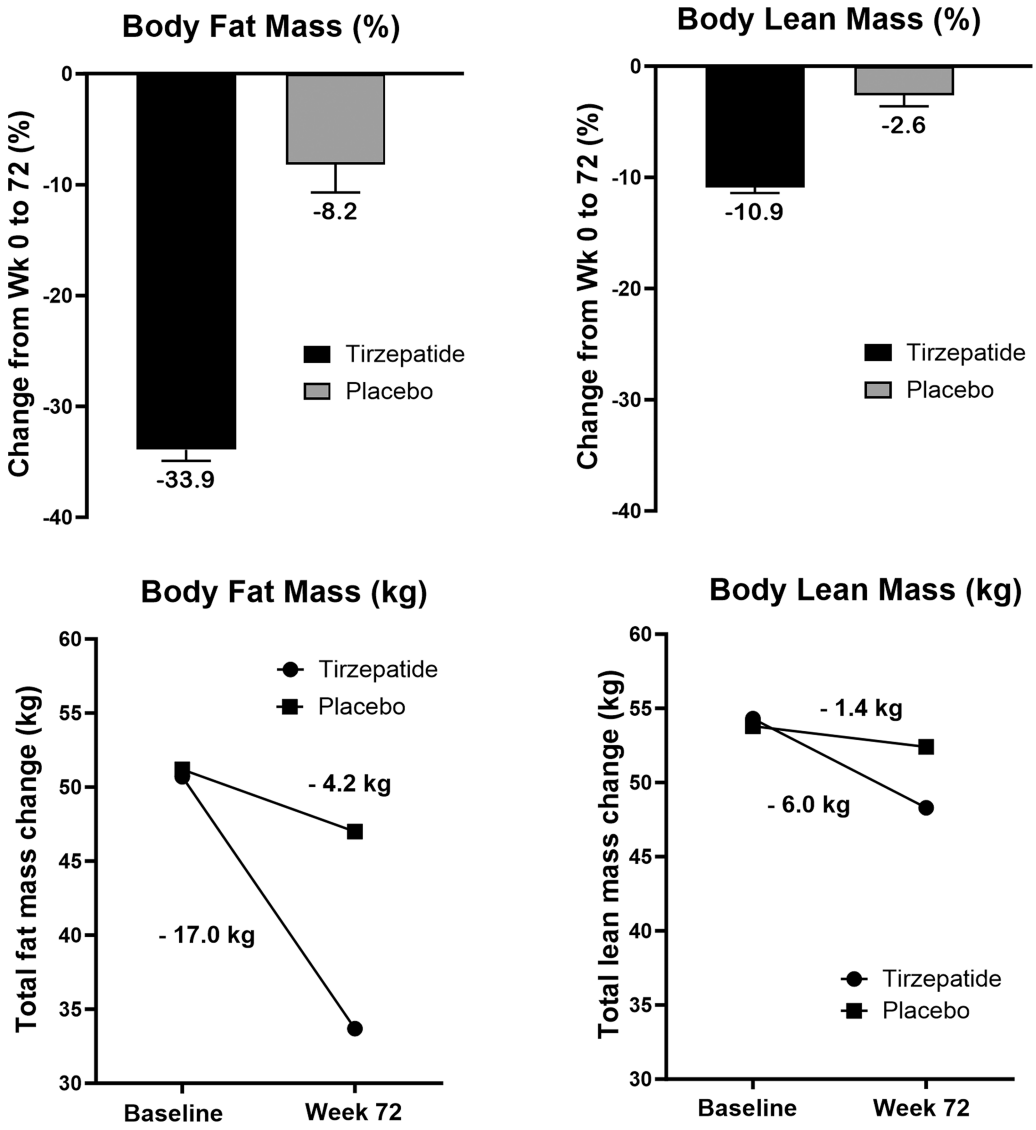

Figure 2—Changes in body composition after 72 weeks of Tz treatment (Study of Tirzepatide [LY3298176] in Participants With Obesity or Overweight [SURMOUNT-1]) and placebo-matching control in a subsample of 160 individuals using DXA. Images are based on data from Jastreboff et al. (20).

sedentary men with obesity (51 ± 7 years, BMI >25 kg/m^2) (59) indicated that, despite no significant changes in body weight, RT increased LM by 1.29 kg (or 2%) while ET decreased LM by 1.08 kg (−1.7%).

A recent study investigated the effects of RT, ET, and their combination on body composition in 160 elderly individuals (70 ± 5 years) with overweight and obesity (BMI ≥30 kg/m^2) undergoing a diet. Despite similar and significant body weight loss (9% average) and fat mass loss (6.9% average) compared with baseline values between groups, RT resulted in less LM loss (−1 kg or −2%) than combination therapy (−1.7 kg or −3%) and ET (−2.7 kg or −5%) (60). In 94 premenopausal women (35 ± 6.2 years) who were overweight (BMI 27–30 kg/m^2), after 1 year of dietary intervention, RT improved fat-free mass (+0.3 kg, or 0.6%), whereas ET (−1.0 kg or −2.2%) and no exercise training (−1.5 kg or −3.1%) reduced fat-free mass (61). To place the relevance of these differences in context, aging-related reduction in LM in older individuals ranges from 1 to 3 kg per decade (34,53), depending upon age and other factors. Collectively, this evidence supports RT as an effective approach to increase or maintain LM or at least mitigate the decrease of LM associated with diet interventions.

Impact of Sex

A recent systematic review concluded that larger improvements in LM are found after RT in males (+1.7 kg, 95% CI 0.5–2.8 kg) than females (+0.8 kg, 95% CI 0.7–1.0 kg) (62). The RT studies reviewed in this analysis had a median duration of 12 weeks (10–16 weeks) and median frequency of 3 sessions/week, and the parameters involved 72 sets/week at an average intensity of 80% of 1 repetition maximum (75% to 85% of 1 repetition maximum) (62). A study of 23 older individuals (71 years) observed that, after 18 weeks, RT increased knee extensor maximal torque by 41.7% in men and 15.8% in women. Differences in muscle quality were also reported, whereby muscle quality increased by 33.7% in males compared with 8.8% in females (63). Furthermore, an RT study of individuals (~70 years)

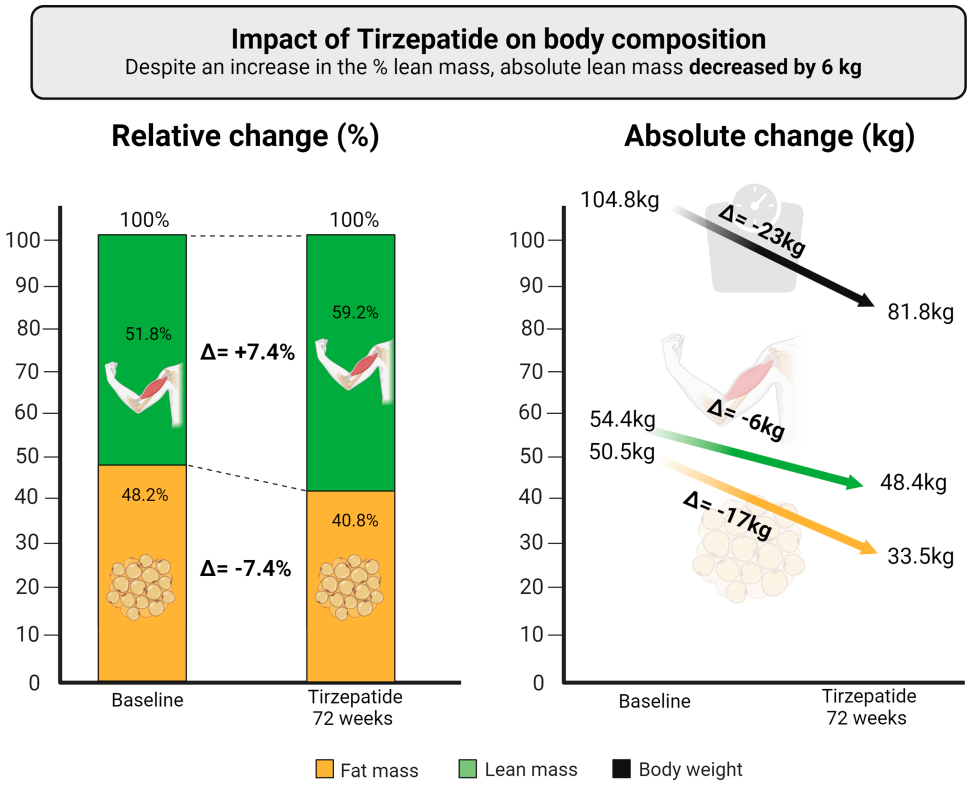

Figure 3—Impact of Tz on body composition: relative versus absolute change. Despite an increase in the percent LM, absolute LM decreased by 6 kg.

with presarcopenia (based on appendicular LM index) observed no significant differences between males and females in LM but that only males significantly improved their strength (64). This body of evidence points to a possible sex difference in the magnitude of change in LM and muscle quality and power after RT interventions. Interestingly, a systematic review and meta-analysis specific to individuals with overweight and obesity (≥18 years) found no differences between males and females for muscle strength after RT (effect size 0.07 ± 0.06; P = 0.31) (65). Therefore, the sex difference in responses to RT seen in older and presarcopenic adults was less apparent in the setting of overweight and obesity.

Impact of Age

Larger improvements in LM have been reported after RT in younger (+1.7 kg, 95% CI 1.0–2.4 kg) compared with older adults (+0.9 kg, 95% CI 0.8–1.1 kg), although both groups benefited (62). In middle-aged to older participants (age ≥50 years), a systematic review showed a positive effect on lean body mass, with a mean LM change of +1.1 kg in interventions with durations between 10 and 52 weeks (mean duration 21 ± 9 weeks), frequency of 2–3 times/week, and intensity ranging from 50 to 80% of 1 repetition maximum (66). A meta-analysis of observational studies by Thomas et al. (67), which included data from 745 postmenopausal and older women (65.8 ± 4.9 years) undertaking a variety of RT protocols (mean duration 16 weeks, 3 days/week, 7 exercises/session), reported significant increases that were small to moderate in size (+0.44 kg) in LM regardless of age, intervention period, weekly training frequency, and number of exercises (67). While all 26 studies reviewed in this analysis showed increases in LM, the impact on LM ranged from 0.2 to 4 kg. This emphasizes the fact that the impact of RT depends critically on the optimization and individualization of the intervention.

Impact on Diet-Related Weight Loss

An overview of 12 systematic reviews and meta-analyses summarizing the impact of exercise training (with or without diet) on body composition during weight loss reported significant weight (−1.5 to 3.5 kg) and fat mass (−1.3 to 2.6 kg) losses in response to exercise training (68) but no net increase in LM. However, RT reduced the loss in LM by 0.8 kg in comparison with diet only. The reported impacts of exercise on LM may have been less apparent because of the diverse forms of exercise included in this analysis. Another systematic review and meta-analysis, which summarized six articles regarding the impact of RT on diet-induced loss in LM mass, concluded that adding RT to diet attenuated the loss of LM by 93.5%, with an absolute difference in LM of approximately 1 kg. Similar reductions in fat mass and body weight were reported between RT-with-diet and diet-alone groups (69) (Fig. 4).

A study comparing the independent and combined effects of caloric restriction and exercise in 107 elderly (70 years) individuals with obesity reported that, after 12 months, the exercise group increased LM by 2.3% (+1.3 kg), while the diet-plus-exercise and diet-only groups experienced decreases in LM of 3.1% (−1.8 kg) and 5.2% (−3.2 kg). The increase in LM of 1.3 kg supports the beneficial impact of exercise on LM (70), and the authors concluded that adding an exercise program to a diet regimen may be the best treatment for older adults with obesity, since this preserves lean body mass in addition to reducing fat mass. In another study that evaluated the effects of adding RT to a hypocaloric diet in frail adults with obesity (70 years) (71), similar body weight

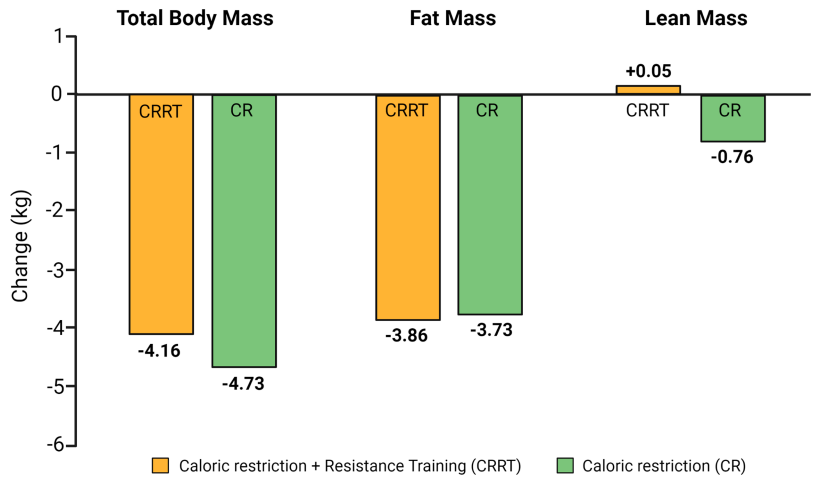

Figure 4—Effects of caloric restriction combined with resistance training versus caloric restriction alone on body composition. Data are from Sardeli et al. (69).

loss occurred between diet and diet + RT groups (10.7 vs. 9.7 kg), along with similar fat loss (6.8 vs. 7.7 kg), but the diet + RT group experienced less fat-free mass reduction than the diet-only group (1.8 vs. 3.5 kg, a difference of 1.7 kg) (71). Bouchard et al. (72) also demonstrated that adding RT to caloric restriction prevented the loss of ∼1 kg of LM that occurred in the diet-only group in 48 women (63 years) with obesity (>35% body fat).

Relationship to Strength

LM loss is related to loss of strength and function in humans. Studies indicate that, from the third to fourth decade onwards, aging is accompanied by loss of strength of around 2.5–4.0% per year (73), with leg strength declining despite habitual endurance exercise in active older adults (74). While the findings described above indicate that RT prevents LM loss with aging, it is unclear whether RT also prevents strength deficits.

Summary

The studies described above reveal that supervised RT interventions with a duration above 10 weeks, a frequency of up to 2–3 times/week, an intensity range between 50 and 80% of 1 repetition maximum, and a minimum of seven exercises/session (e.g., large muscle groups) elicit improvements in LM acquisition and/or maintenance in aging men and women, with an average increase of approximately 1.1 kg. Evidence also indicates that RT can effectively mitigate LM or skeletal muscle mass loss associated with dietary interventions (75) and in response to disease states (76). This occurs independently of reductions in body weight and fat mass. The absolute magnitude of RT impact in terms of LM mitigation depends upon factors such as whether the exercise is combined with protein supplementation or whether the LM loss is induced by diet (∼1-kg effect) or disease (>1-kg effect). It appears that mitigation is larger in absolute terms under circumstances where greater loss of muscle mass occurs in the untrained comparator group. This suggests that compensation for LM loss is effective using RT, but overcompensation (i.e., increase in mass rather than prevention of loss) does not typically occur.

CAN EXERCISE TRAINING PRESERVE LM AND FUNCTION IN INDIVIDUALS TAKING INCRETIN THERAPY?

The effect of exercise training in participants administered incretin therapy was assessed by Lundgren et al. (77). They evaluated the effect of exercise training and Lira, a first-generation GLP-1RA. After an initial 8-week period of caloric restriction during which participants with obesity lost an average of 12% (∼13 kg) of their initial body weight, 5.1 kg LM, and 7.3 kg fat mass, this study randomized 195 participants (42 ± 12 years) to four groups: placebo, exercise (combined training), Lira alone, or Lira + exercise (Fig. 5). The exercise program was designed to meet the World Health Organization (WHO) recommendations of a minimum of 150 min per week of moderate-intensity aerobic physical activity, 75 min per week of vigorous-intensity aerobic physical activity, or an equivalent combination of both.

After 12 months, greater weight loss was observed in the combination group (Lira + exercise, 3.5% or −3.4 kg) than the Lira-only group (0.7% or −0.7 kg). The exercise-only group increased body weight by 2% (+2.0 kg). Better results in the combined group were also found in terms of fat loss, with a reduction of 3.5% (−4.7 kg), approximately twice the decrease in the exercise group (−1.8% or −1.4 kg) and the Lira group (−1.6% or −2.0 kg) (77). The exercise group increased LM by 3.4% (+2.1 kg) compared with the Lira group (0.0 kg; 95% CI −1.0 to 1.1), while the combination group also exhibited an increase of 0.8% (+0.5 kg). A subsequent analysis from the same study showed that the combination of exercise and Lira increased cognitive restraint score (13% vs. −9%; $P = 0.042$), reflecting a conscious restriction of food intake and decreased sedentary time (−10 vs. 31 min/day; $P = 0.049$) compared with placebo, possibly facilitating additional weight loss (78). Both cognitive restraint and moderate to vigorous physical activity were associated with less weight regain. This study examined weight loss maintenance following an initial low-calorie diet phase, and it reported modest effects of subsequent Lira treatment on weight loss (0.7 kg) and loss of LM (0.0 kg). It was not designed to evaluate the effects of combining exercise and incretin treatment as the primary weight loss therapy. It is also relevant that the exercise intervention involved ET rather than RT and that Sema and Tz have much larger impacts on weight and LM loss than Lira (79).

Where LM is the focus, RT is a more effective intervention than ET, yet there are currently no studies in the literature that have used individually tailored RT interventions in combination with incretins. Based on well-established effects on LM in obesity, sarcopenia, and type 2 diabetes, it is plausible that RT would mitigate LM loss, and perhaps promote greater fat mass loss, in participants administered incretin therapy. While definitive studies are lacking, based on studies conducted in different clinical settings, we propose that RT may be a key intervention that, when performed in conjunction with incretin treatment, could improve body composition and provide additional health benefits.

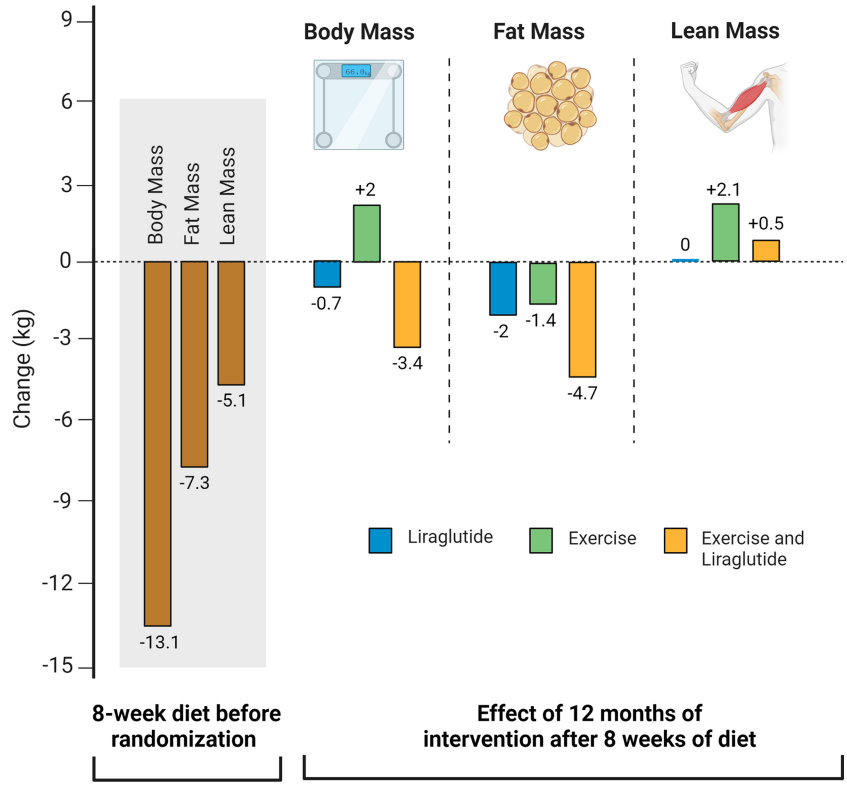

Figure 5—Effects of Lira combined with exercise on body composition. Data are from Lundgren et al. (77).

CAN MAINTENANCE OF LM PREVENT REBOUND WEIGHT GAIN AFTER INCRETIN THERAPY?

While incretin pharmacotherapies are very effective for inducing weight loss, extensive diet literature indicates that weight is rapidly regained on cessation of energy intake restriction (80). This also appears to be true of incretin therapies. A recent report indicated that, in middle-aged (49 ± 12 years) individuals with obesity (BMI ≥30 kg/m^2) (81), 68 weeks of Sema therapy induced mean weight loss of 17.3% (−18.3 kg) vs. 2% (−2.1 kg) for placebo, but 52 weeks after therapy, participants had regained 67% (+12.2 kg) of their lost weight.

In a previous study that compared the effects of continuing versus withdrawing Sema treatment on body weight in middle-aged adults (47 ± 12 years) with overweight and obesity, an initial 20-week Sema (2.4 mg) administration reduced body weight by 10.6% (−11.1 kg) (82). Thereafter, an additional body weight reduction of 7.9% (−7.1 kg) was reported for those maintained on Sema treatment until 68 weeks, whereas the group that discontinued treatment at 20 weeks demonstrated body weight regain of 6.9% (6.1 kg) (82). This represents a weight regain of 55% of their initial total body weight loss, broadly consistent with the 67% regain in the Semaglutide Treatment Effect in People with Obesity (STEP 1) follow-up described above (81).

Finally, a recent study compared the effects of continued Tz versus placebo in middle-aged adults (48 ± 13 years) with overweight and obesity (83). After a 36-week lead-in involving Tz treatment (10 mg or 15 mg), which induced weight reduction of 20.9% (−22.1 kg), individuals were randomized to continued Tz treatment for another 52 weeks (additional weight reduction of 5.5% or −4.7 kg, totaling −25.8%, or −26.8 kg, over the 88-week treatment period) or placebo injections (regaining 54.5%, or 12 kg, of the total body weight loss during the 36-week lead-in). The level of weight regain in the placebo group was broadly consistent with the 67% and 55% body weight regain after Sema discontinuation described above.

It is likely that weight regain following incretin cessation is impacted by the magnitude of LM loss induced by that therapy. As described above, muscle mass is highly metabolically active, with muscle loss linked to decreased metabolic rate (84). We speculate that for this reason, the diminution in LM during incretin therapy would predispose to rapid weight, and fat, regain, where energy intake increases following discontinuation of pharmacotherapy. Figure 6 illustrates this proposal. Here, we assume that incretin therapies induce an average of ∼17% weight loss (combined data from Wilding et al. [17] and Jastreboff et al. [20]), and treatment discontinuation results in ∼60% of the weight loss being regained (81,83). If incretin therapy is combined with RT, a smaller reduction in body weight may occur as a result of LM retention (Fig. 6*A*). Regarding fat mass, evidence suggests a decrease of ∼29% after incretin therapy (17,20), and we hypothesize ∼66% fat mass regain after discontinuation of treatment. We also hypothesize increased fat loss when incretin therapy is combined with RT on the grounds that RT promotes higher LM retention and, hence, energy expenditure (Fig. 6*B*). LM is highly metabolically active, so its retention during incretin therapy may also result in less fat regain after treatment cessation. Incretin therapy induces an average LM loss of ∼13%. Hence, if RT prevents loss of LM associated with incretin therapy, less fat rebound would occur after treatment discontinuation (Fig. 6*C*). In these schema, preservation of LM because of RT during incretin treatment prevents rebound gain of weight and fat after cessation of pharmacotherapy for obesity.

CONCLUSIONS

Obesity costs OECD (Organization for Economic Cooperation and Development) countries around 8% of their total health care funding, and every dollar spent on obesity prevention returns approximately $7 (85). It has been estimated that optimizing the benefits of exercise has the potential to raise global gross domestic product by US$600 billion per annum (87). In data specific to the benefits and costs of exercise provision in type 2 diabetes in the Australian health care system, in which accredited exercise physiologists are employed as allied health professionals to deliver exercise therapy in collaboration with primary health care professionals, it was calculated that total well-being benefits amounted to $8,000 per person treated, while the cost of exercise provision was $580. The impact of RT when using incretin-based agents to lose body weight in obesity

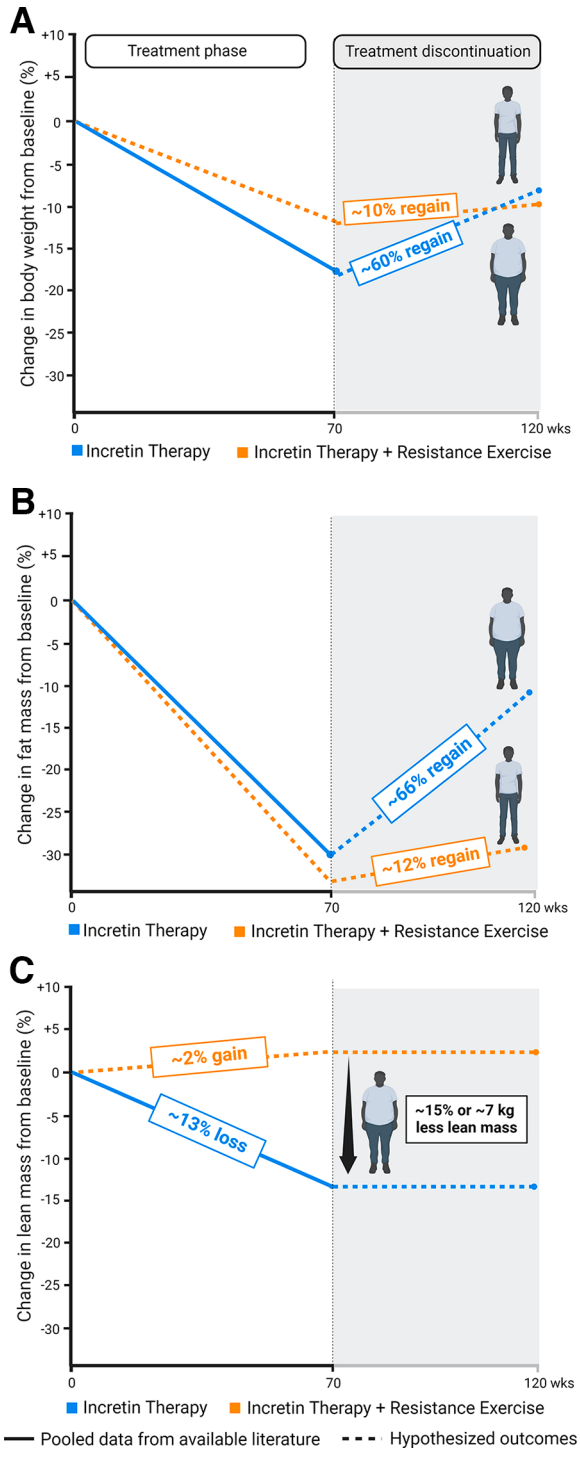

Figure 6—Hypothesized effects of incretin therapy with and without resistance training (RT) and its discontinuation on body weight (*A*), fat mass (*B*), and LM (*C*). Incretin therapy induces an average of ∼17% weight loss (combined data from Wilding et al. [17] and Jastreboff et al. [20]). After treatment discontinuation, ∼60% of the weight loss is regained (81,83). If incretin therapy is combined with RT, we hypothesize that smaller body weight reduction may occur due to LM retention. Regarding fat mass, evidence suggests a decrease of ∼29% after incretin therapy (combined data from Wilding et al. [17] and Jastreboff et al. [20]), and we hypothesize ∼66% fat mass regain after discontinuation of treatment. We hypothesize increased initial fat mass loss where incretin therapy is combined with RT on the grounds that RT promotes higher LM retention and hence energy expenditure. LM is highly metabolically active, so its retention during incretin therapy may mean that less fat is regained after treatment cessation. Furthermore, incretin therapy induces an average LM loss of ∼13%. RT should prevent loss of LM associated with incretin therapy, with less fat rebound after treatment discontinuation.

and type 2 diabetes likely approximates this benefit-to-cost ratio, exceeding 9:1 (86).

Incretin-based therapies have rapidly become a global focus of obesity treatment and management because of the substantial weight loss elicited by these drugs in the context of relatively moderate side effects. Recent evidence indicates that incretin therapy decreases cardiovascular end points in patients with obesity (18). However, it is germane that while the weight loss is primarily fat, a considerable amount is lean or muscle mass. The magnitude of LM loss associated with some incretin therapies exceeds that seen during 10 years of aging, which may be particularly clinically relevant following longer-term therapy and/or in patients who are older and prone to sarcopenia (88). This profound level of LM loss would be expected to have deleterious impacts on health outcomes, including frailty and long-term mortality risk, which may be particularly relevant in older adults.

In summary, effective loss of excess weight conveys multiple health benefits, including a reduction in cardiovascular risk. However, the salutary effects of incretin therapies on fat loss may be offset by decreases in skeletal muscle mass, potentially compromising the longer-term health benefits associated with this class of drugs. RT increases skeletal muscle mass and strength and prevents muscle loss that results from dieting and disease. RT-based preservation of skeletal muscle mass during incretin therapy may also prevent rebound weight and fat gain in those who cease pharmacotherapy. Future studies will be required to vindicate this proposition and to directly address the impacts of RT on body composition changes in patients undergoing incretin therapy. However, exercise is nonpharmacological and has multiple health benefits, and there is evidence for its effectiveness as an intervention in other contexts. Therefore, we advocate that tailored RT programs should be adopted without delay in patients embarking on incretin therapy.

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