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Body composition changes during weight reduction with tirzepatide in the SURMOUNT-1 study of adults with obesity or overweight

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Abstract

Aims: We assessed changes in body composition following tirzepatide treatment in a substudy of participants with obesity or overweight from the SURMOUNT-1 trial, overall and post hoc in clinically relevant subgroups.

Materials and Methods: Substudy participants ($n = 160$ of the 2539 in SURMOUNT-1) underwent dual-energy X-ray absorptiometry (DXA) at baseline and Week 72. Body composition parameters were evaluated by analysis of covariance, logistic regression or Fisher's exact test. Post hoc subgroup analyses were conducted by sex (female or male), age (<50, 50 to <65, or ≥65 years) and total body weight reduction tertiles (≤15.3 kg, >15.3 to ≤25.9 kg, or >25.9 kg).

Results: The 160 participants (pooled tirzepatide doses $n = 124$, placebo $n = 36$) with baseline and end of study DXA data were 73% female and had a mean weight of 102.5 kg and body mass index of 38.0 kg/m^2. The change in body weight, fat mass and lean mass from baseline to Week 72 was −21.3%, −33.9% and −10.9% with tirzepatide and −5.3%, −8.2% and −2.6% with placebo, respectively ($p < 0.001$ for all comparisons). Of the body weight lost, approximately 75% was fat mass and 25% was lean mass for both tirzepatide and placebo. These proportions remained consistent across most subgroup analyses.

Conclusions: In participants with obesity or overweight from the SURMOUNT-1 trial, tirzepatide treatment significantly reduced body weight, fat mass and lean mass compared with placebo, while in post hoc analyses, the proportion of body weight lost as fat or lean mass was relatively consistent including in clinically relevant subgroups.

KEYWORDS
dual-energy X-ray absorptiometry, fat mass, lean mass, obesity, tirzepatide

1 | INTRODUCTION

The United States is decades into an obesity epidemic, and its negative impact on the healthcare system and broader society is well established.[1] Individuals living with obesity have the burden of an increased risk of premature mortality and developing over 200 possible complications and comorbidities, as well as impaired quality of life.[2] Obesity has been defined as a 'highly prevalent chronic disease characterized by excessive fat accumulation or distribution that presents a risk to health'.[3] Clinical trials for obesity management medications (OMMs) approved for weight management primarily focus on body weight reduction due to regulatory agency requirements.[4] This approach aligns with clinical practice where body weight, body mass index (BMI) and waist circumference are the most commonly applied anthropometric measurements. However, as obesity is a disease of excess adiposity, understanding changes in fat mass and overall body composition during obesity management is clinically relevant.

Weight reductions of 2%–5% improve some obesity-related complications and quality of life; however, certain complications require weight reductions of over 15%.[5,6] Total body weight reduction includes decreases in both fat mass (total body mass of all fat molecules in the body) and lean mass (total body fat-free mass minus total bone mineral content, also known as lean soft tissue mass).[7] Excessive lean body mass loss, particularly skeletal muscle loss, may result in reduced physical function, muscle strength, resting energy expenditure and neuromuscular function, along with increased fatigue and risk for injury.[8,9] Many dietary restriction studies report that fat mass loss contributes to approximately 75% of body weight reduction, while lean mass loss contributes to 25% of body weight reduction.[8]

The body composition of fat mass and lean mass is influenced by sex and aging, and fat mass is a standard component when assessing body composition. The percentage of body fat mass ranges between 15% and 29% in healthy females and 10% and 24% in healthy males.[10] Age is also an important factor influencing fat mass and other body composition measures. As humans age, there is an increase in fat mass coupled with a gradual decline in lean mass, specifically muscle mass.[11,12] While this change is a natural component of aging, it can lead to pathology, such as an increased risk of developing sarcopenia.[12]

Recently approved OMMs are contributing to an emerging modern era of obesity care, and a better understanding of the effects of these treatment options can enhance clinical decision-making. Tirzepatide is a once-weekly single molecule that activates the glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors and is approved for treatment in adults with obesity or overweight with a weight-related complication (e.g., hypertension, dyslipidemia, obstructive sleep apnea or cardiovascular disease) and in adults with type 2 diabetes. In the SURMOUNT-1 phase 3, randomized, double-blind, placebo-controlled trial in participants with obesity or overweight, the mean change in body weight was −16.0% (5 mg), −21.4% (10 mg) and −22.5% (15 mg) in tirzepatide-treated participants relative to −2.4% in placebo-treated controls at 72 weeks of treatment.[13] It is unknown if the greater weight reductions observed with tirzepatide result in excessive loss of lean mass; therefore, the present SURMOUNT-1 dual-energy X-ray absorptiometry (DXA) substudy further evaluated body composition changes in participants receiving tirzepatide or placebo, including in clinically relevant subgroups.

2 | MATERIALS AND METHODS

2.1 | Study design

The present report is a SURMOUNT-1 DXA substudy. The study design and results of the SURMOUNT-1 trial (NCT04184622) have been previously reported.[13] Briefly, SURMOUNT-1 was a phase 3, multicenter, double-blind, placebo-controlled trial that investigated the effects of once-weekly tirzepatide (5, 10 or 15 mg) versus placebo (randomized 1:1:1:1) over 72 weeks for weight management in adults without type 2 diabetes with a BMI ≥30 kg/m^2 or ≥27 kg/m^2 with one or more weight-related complication(s). Participants received individualized lifestyle counselling delivered by a dietitian or a qualified health care professional with goals of a 500 kilocalorie/day dietary deficit and were advised to increase their physical activity to at least 150 min/week without a specific strength training protocol.

Body composition was assessed in the participants enrolled in the present DXA substudy by whole-body DXA. The 28 DXA trial sites included sites in Argentina, Brazil, Mexico, Puerto Rico, Taiwan and the United States. The overall study and the substudy were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and were approved by an independent ethics committee or institutional review board at each trial site. All the participants provided written informed consent for the SURMOUNT-1 trial and the substudy before participation. Randomization from the overall trial was applied to the substudy.

2.2 | Participants

All participants in SURMOUNT-1 were eligible for the substudy until the required number of participants were enrolled at sites that had access to whole-body DXA scanners with body composition capability. Key exclusion criteria were having undergone a recent procedure where oral contrast or radionuclides were administered or having (according to the DXA manufacturer's specifications) a body weight, height and/or width that did not allow acquisition of accurate DXA measurements or implants, hardware or devices that could interfere with the scan.

2.3 | Procedures

Baseline DXA scans were performed at the time of randomization in the main study protocol, before the first dose of study drug was administered. End-of-treatment DXA scans were performed at or within 14 days of Week 72 or early discontinuation study visits. DXA scans were performed on either Hologic™ or GE HealthCare/Lunar™ DXA scanners with total body composition capabilities following the central

TABLE 1 Body composition definitions.

Term	Technical definition	Colloquial definition
Fat mass	Estimated mass of all fat molecules in the body	Estimated mass of all adipose tissue
Fat-free mass	Estimated mass of all nonfat molecules in the body (includes muscles, bones, organs, ligaments, tendons and water). Note that fat-free mass was not evaluated in the present study.	Estimated mass of tissue that is not adipose
Lean mass	Fat-free mass minus total bone mineral content (also known as lean soft tissue mass)	Estimated mass of tissue that is not adipose and exclusive of bone mineral content
Visceral fat mass	Estimated mass of all fat molecules in the android region minus estimated mass of all fat molecules in the subcutaneous adipose portion of the android region	Estimated mass of adipose tissue in the android region (the lower 20% of the trunk region) minus estimated subcutaneous adipose tissue in the android region
Proportion of body weight reduction as fat mass[a]	The percentage of total body weight reduction from fat mass	
Proportion of body weight reduction as lean mass[a]	The percentage of total body weight reduction from lean mass	

Note: Terms associated with dual-energy X-ray absorptiometry measurements. Sargeant et al.,[40] Holmes et al.[12] and Tinsley and Heymsfield.[7]

[a]The formula for the proportion of total body weight reduction that is fat mass is fat mass loss/(fat mass loss + lean mass loss). For example, if a subject loses 10 kg of body weight, of which 7.5 kg is fat mass and 2.5 kg is lean mass, then the proportion of fat mass loss is 75% and the proportion of lean mass loss is 25%.

imaging vendors' provided guidelines and manufacturer's recommendations. Both Hologic and Lunar DXA scanners were used and are considered highly concordant for fat mass and lean mass (i.e., lean soft tissue).[14] Standard outputs of fat mass and lean mass were obtained, and estimates of visceral fat mass from the android region (henceforth, visceral fat mass) were automatically generated from the DXA manufacturer software (definitions; Table 1). Visceral fat mass was estimated as the lower 20% of the trunk region from DXA manufacturers' algorithms. Waist circumference was measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest and rounded to the nearest 0.5 cm. All scans were evaluated and interpreted by a blinded central reader. Detailed instructions on the DXA scan protocol were provided to study sites. These instructions included that all scans for a given participant be performed on the same DXA scanner using the same software and under similar circumstances (similar time of day, consistent hydration status, similar positioning).

2.4 | Endpoints

The primary objective of the substudy was to assess whether pooled tirzepatide (5, 10 and 15 mg combined) was superior to placebo in the percent change in fat mass from baseline to Week 72. Key secondary endpoints for pooled tirzepatide doses included the percent change from baseline in lean mass and the absolute change from baseline in lean and fat mass. Exploratory endpoints were post hoc analyses that included the percent change from baseline in body weight, visceral fat mass and waist circumference and the proportion of body weight reduction as fat mass and lean mass (henceforth, the proportion of fat mass loss or lean mass loss; Table 1). In post hoc analyses, changes in fat mass and lean mass were also evaluated by subgroups of age, sex and body weight reduction tertiles, as they are clinically pertinent.

2.5 | Statistical analyses

A sample size of 240 participants (60 participants from each treatment arm) was calculated to provide more than 90% power to demonstrate that pooled tirzepatide doses once weekly were superior to placebo in percent change in fat mass loss from baseline to Week 72 at a two-sided significance level of 0.05 using a two-sample t test. The sample size calculation assumed a treatment difference of at least 4.8% with a common standard deviation of 8% in the percent change of fat mass and a dropout rate of 25% at Week 72.

Analyses were conducted on all substudy participants who were randomized and received at least one dose of study drug, with both nonmissing baseline and postbaseline DXA measurements. Missing data at Week 72 from three participants were imputed using the last observation carried forward method.[15,16] There was no multiplicity adjustment. The analysis of covariance model was used to analyse continuous outcomes, with baseline value of the response variable as a covariate and treatment group as a factor. Summary statistics for categorical measures included sample size, frequency and percentages. Logistic regression was used to examine the treatment difference in binary outcomes if adjustment for covariates was needed. Otherwise, Fisher's exact test was used to examine treatment differences in categorical outcomes.

3 | RESULTS

3.1 | Patients

A total of 255 participants enrolled in the SURMOUNT-1 DXA substudy (Figure S1). Of these, 160 completed baseline and Week 72 or early discontinuation DXA scans and were included in the efficacy analyses.

Demographic and clinical baseline characteristics were generally similar across treatment groups (Table S1). The mean age of the DXA substudy participants was 46.2 years, 73.1% were female and 75.6% were White. At baseline, participants had a mean body weight of 102.5 kg, BMI of 38.0 kg/m^2 and waist circumference of 111.5 cm. The

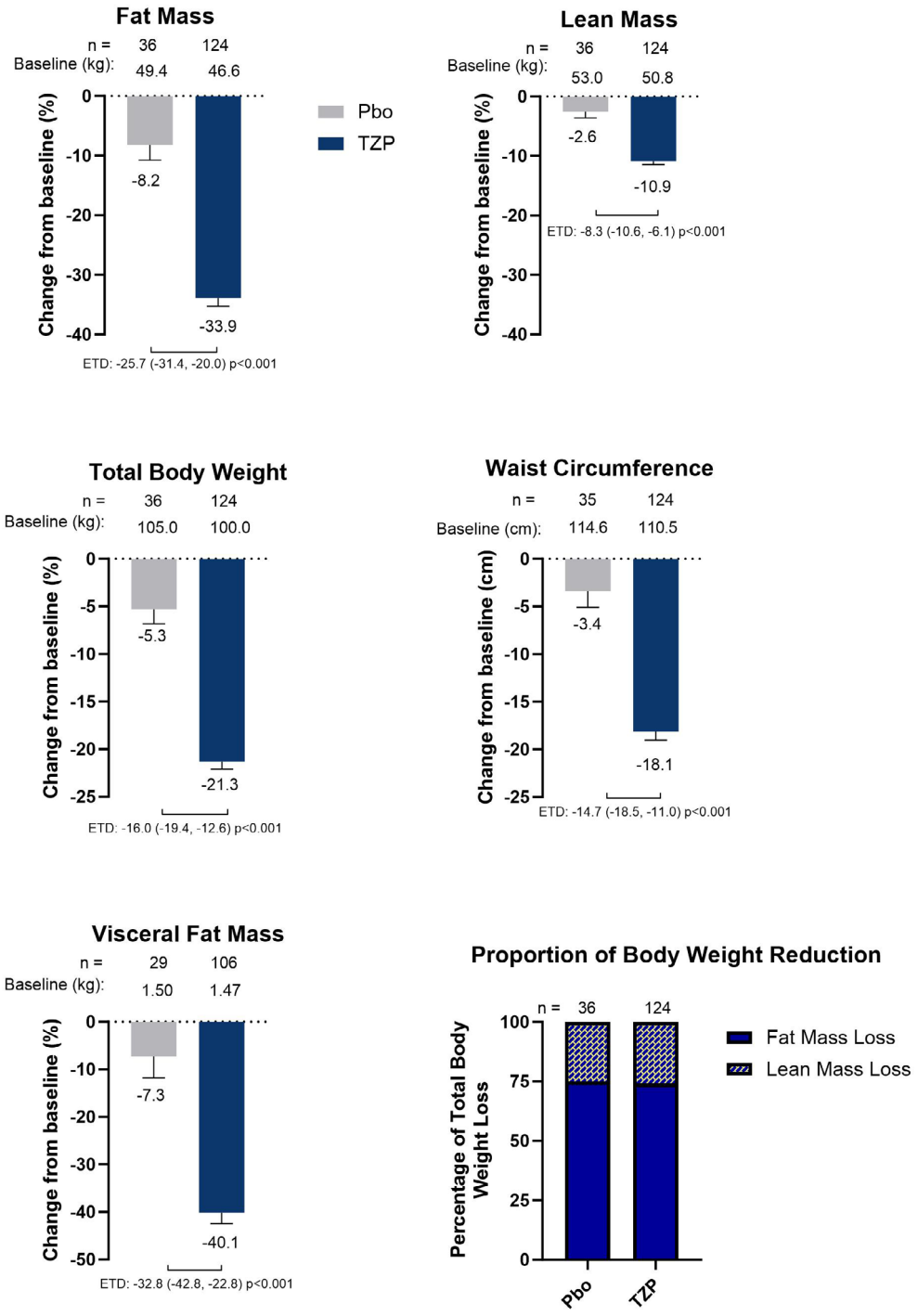

FIGURE 1 Change in body composition at Week 72. Data are least squares means (standard error) for change from baseline, modified intent-to-treat population (efficacy analysis set). Data are shown for placebo and pooled tirzepatide 5, 10 and 15 mg groups. ETDs are least squares means (95% confidence interval) versus placebo. Waist circumference data are mixed model for repeated measures, and other body composition measures data are analysis of covariance model for postbaseline measures. ETD, estimated treatment difference; *n*, number of participants with baseline and postbaseline data; Pbo, placebo; TZP, pooled 5/10/15 mg tirzepatide.

average duration of obesity was 14.9 years, and 33.1% had prediabetes at baseline (Table S1). The average fat mass at baseline was 46.6 kg in participants who received tirzepatide (pooled 5, 10 and 15 mg doses) and 49.4 kg in participants who received placebo (Figure 1). The average lean mass at baseline was 50.8 and 53.0 kg in participants who received tirzepatide (pooled doses) and placebo, respectively.

3.2 | Change in body composition

Mean percent change in fat mass at Week 72 was −33.9% with pooled doses of tirzepatide, compared with −8.2% with placebo, for an estimated treatment difference (ETD) relative to placebo of −25.7% (95% confidence interval [CI]: −31.4, −20.0; $p < 0.001$; Figure 1). Mean change in lean mass was −10.9% with tirzepatide, compared with −2.6% with placebo (ETD: −8.3 [95% CI: −10.6, −6.1] $p < 0.001$). Mean absolute change in fat mass at Week 72 was −15.9 kg with tirzepatide, compared with −3.6 kg with placebo, for an ETD relative to placebo of −12.3 kg (95% CI: −15.1, −9.6; $p < 0.001$; Figure S2). Mean absolute change in lean mass was −5.6 kg with tirzepatide and −1.2 kg with placebo (ETD: −4.4 [95% CI: −5.6, −3.2] $p < 0.001$).

Change in body weight was −21.3% with tirzepatide and −5.3% with placebo (ETD: −16.0; [95% CI: −19.4, −12.6] $p < 0.001$; Figure 1). Change in waist circumference was −18.1 cm with

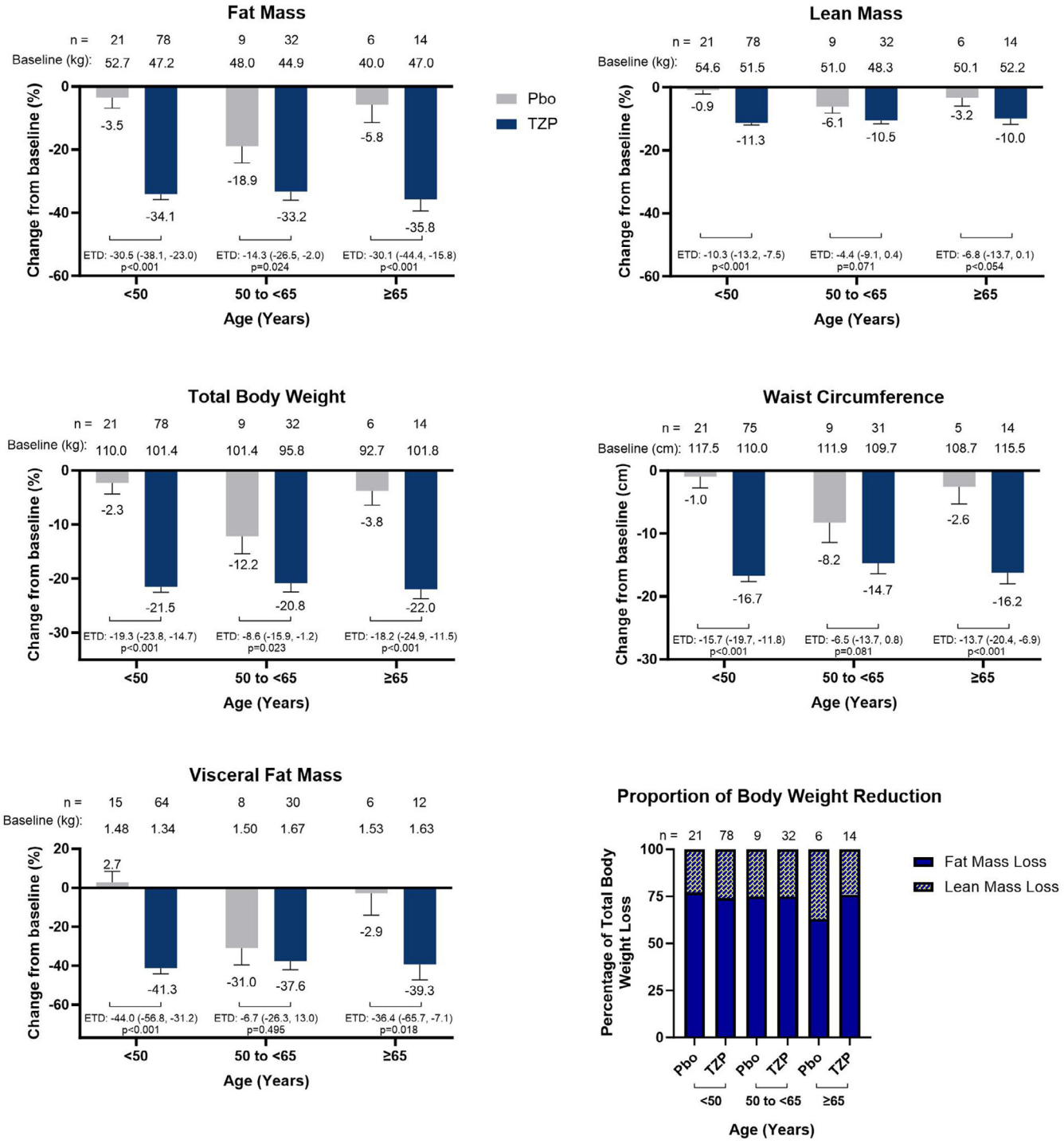

FIGURE 2 Change in body composition by age subgroups at Week 72. Data are least squares means (standard error) for change from baseline, modified intent-to-treat population (efficacy analysis set). Data are shown for placebo and pooled tirzepatide 5, 10 and 15 mg groups. ETDs are least squares means (95% confidence interval) versus placebo. Waist circumference data are mixed model for repeated measures, and other body composition measures data are analysis of covariance model for postbaseline measures. ETD, estimated treatment difference; *n*, number of participants with baseline and postbaseline data; Pbo, placebo; TZP, pooled 5/10/15 mg tirzepatide.

tirzepatide and −3.4 cm with placebo (ETD: −14.7 [95% CI: −18.5, −11.0] $p < 0.001$). Change in visceral fat mass was −40.1% with tirzepatide and −7.3% with placebo (ETD: −32.8 [95% CI: −42.8, −22.8] $p < 0.001$). The proportion of body weight reduction was 74% as fat mass and 26% as lean mass with tirzepatide, while it was 75% as fat mass and 25% as lean mass with placebo.

3.3 | Subgroup analyses

Across analyses of subgroups by age (Figure 2) and sex (Figure 3), tirzepatide was associated with significantly greater body weight and fat mass reductions at Week 72 than placebo. Lean mass was also significantly reduced with tirzepatide compared with placebo for most

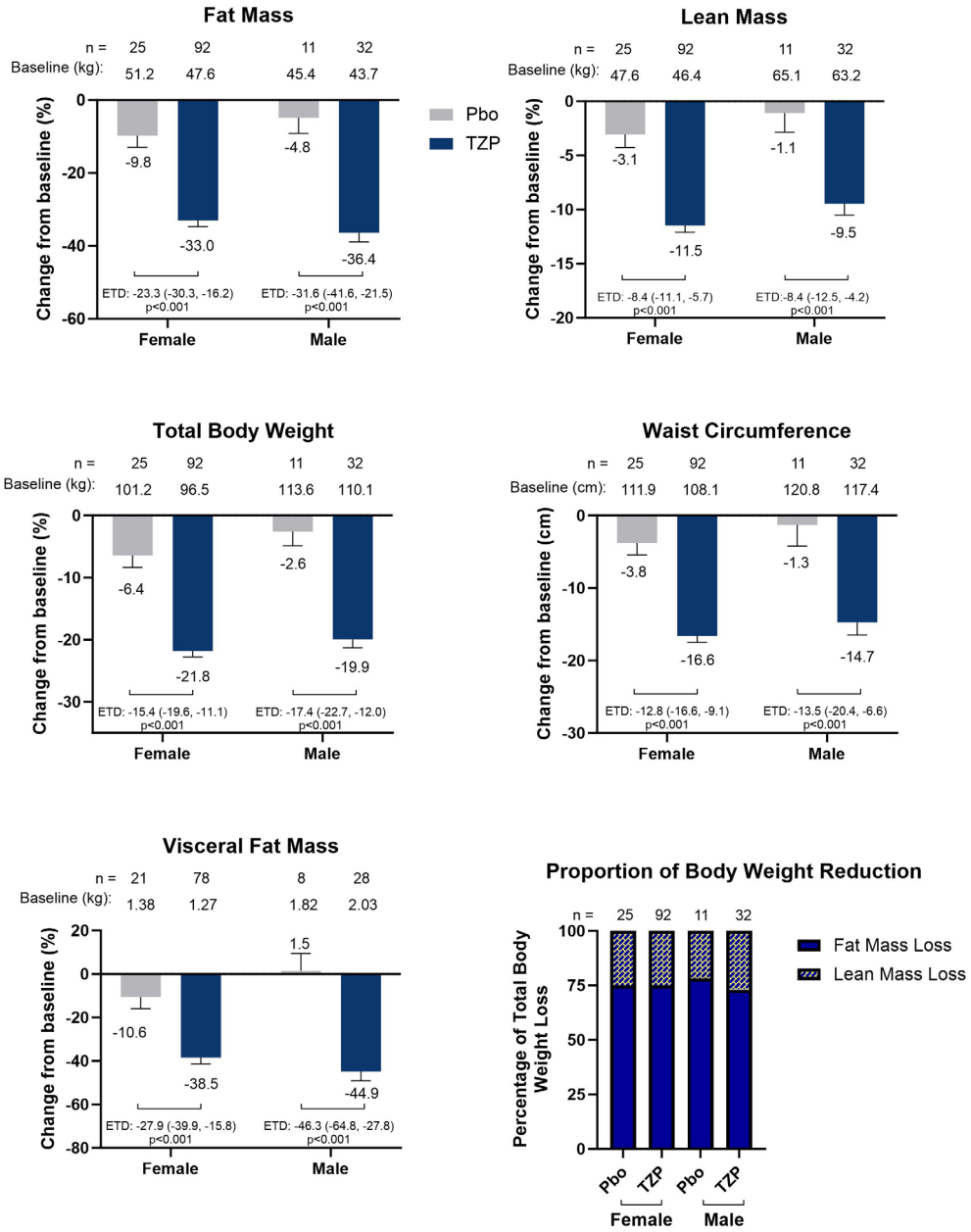

FIGURE 3 Change in body composition by sex at Week 72. Data are least squares means (standard error) for change from baseline, modified intent-to-treat population (efficacy analysis set). Data are shown for placebo and pooled tirzepatide 5, 10 and 15 mg groups. ETDs are least squares means (95% confidence interval) versus placebo. Waist circumference data are mixed model for repeated measures, and other body composition measures data are analysis of covariance model for postbaseline measures. ETD, estimated treatment difference; *n*, number of participants with baseline and postbaseline data; Pbo, placebo; TZP, pooled 5/10/15 mg tirzepatide.

subgroups. Tirzepatide was also associated with greater reductions in waist circumference and visceral fat mass than placebo across the evaluated subgroups (Figures 2 and 3). When treatment effect was compared between sexes within treatment groups, no significant difference was seen for any evaluations of treatment effect, including percent change from baseline (fat mass: $p = 0.228$; lean mass: $p = 0.925$; total body weight: $p = 0.695$; waist circumference: $p = 0.995$; visceral fat mass: $p = 0.108$). For participants who received tirzepatide, the tertiles of total body weight reduction from baseline were ≤15.3 kg, >15.3 to ≤25.9 kg or >25.9 kg. Figure 4 demonstrates that with higher body weight reductions, more fat mass and lean mass were lost.

For all subgroup analyses, the proportion of body weight reduction from baseline was approximately 75% fat mass loss and 25% lean mass loss (Figure S3, also Figures 2–4). Respective to age subgroups of <50, 50 to <65 and ≥65 years, there was 74%, 75% and 76% weight reduction as fat mass loss with tirzepatide and 77%, 75% and 63% as fat mass loss with placebo (Figures S3A and 2). For females and males, respectively, there was 75% and 73% weight reduction as fat mass loss with tirzepatide and 75% and 78% as fat mass loss with placebo (Figures S3B and 3). Respective to the weight reduction tertile subgroups, there was 70%, 73% and 76% body weight lost as fat mass with tirzepatide (Figures S3C and 4). In addition to weight reduction tertiles, the proportion of weight reduction as fat mass by tirzepatide dose was evaluated. The tirzepatide 5, 10 and 15 mg doses resulted in 75%, 72% and 75% body weight lost as fat mass, respectively, consistent with overall findings (data not shown).

4 | DISCUSSION

SURMOUNT-1 study participants with obesity or overweight in the DXA substudy had average weight changes of −21.3% with

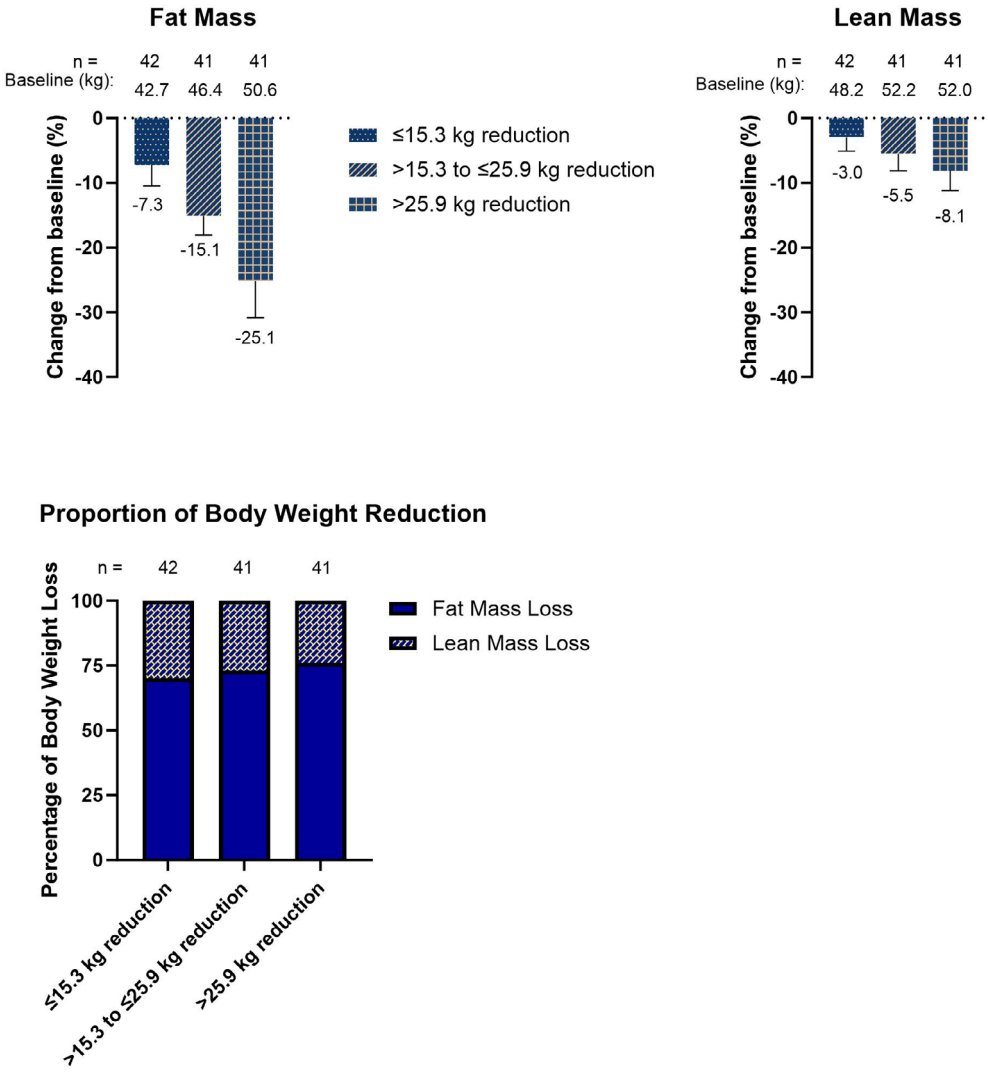

FIGURE 4 Change in body composition by weight reduction tertiles at Week 72 for participants treated with tirzepatide. Participants treated with tirzepatide were grouped into tertiles of total body weight reduction and evaluated for body composition. Data are least squares means (standard error) for change from baseline, modified intent-to-treat population (efficacy analysis set). Data are shown for pooled tirzepatide 5, 10 and 15 mg groups. Body composition measures data are analysis of covariance model for postbaseline measures. *n*, number of participants with baseline and postbaseline data.

tirzepatide compared with −5.3% with placebo, consistent with the overall SURMOUNT-1 study results.[13] Tirzepatide reduced fat mass from baseline by an ETD of 25.7% more than placebo, while lean mass was reduced by an ETD of 8.3% more than placebo. In post hoc analyses, tirzepatide was associated with significantly reduced waist circumference and visceral fat mass compared with placebo. The proportion of weight reduction was 74% as fat mass loss and 26% as lean mass loss, similar to that with placebo (75% and 25%, respectively), despite greater total body weight reduction with tirzepatide than with placebo. These proportions remained consistent across most subgroup analyses by age, sex and weight reduction tertiles, except for 63% of body weight reduction from fat mass in the subgroup aged ≥65 years receiving placebo and 70% reduction from fat mass in the lowest tertile of weight reduction with tirzepatide (≤15.3 kg).

It has been unclear if the greater weight reduction and rate of weight loss induced by highly effective OMMs increase the risk of clinically relevant losses of lean muscle mass that could result in loss of physical function and strength.[17,18] In the SURMOUNT-1 population, tirzepatide significantly improved patient-reported physical function via the Short Form Survey-36 version 2 (SF-36v2) acute form Physical Component Summary, Physical Functioning Domain and Role-Physical Domain compared with placebo.[19] While the SF-36v2 provides participants' subjective responses, these measures are relevant, as they have been shown to predict long-term mortality risk.[20] The positive physical function findings from the SURMOUNT-1 study[19] support results from the current DXA substudy that participants receiving tirzepatide reported improved physical function scores despite decreases in lean mass. A review of bariatric surgery also reported improved physical function despite lean mass loss and found that reductions in body weight and BMI are the strongest predictors of physical improvement.[21] In the analyses of proportional weight loss in the current study, tirzepatide resulted in three times the amount of fat mass loss compared with lean mass loss (75% fat mass loss, 25% lean mass loss), consistent with other therapies.[18] Therefore, similar to indications from the review of bariatric surgery,[21] increased fat mass loss with tirzepatide may have contributed to the greater improvements in overall physical function.

Lean mass decrease may be undesirable for older adults with or at risk of developing sarcopenic obesity. Consistent with results of

studies of caloric restriction and lifestyle intervention-induced weight loss in older adults,[11] tirzepatide was not associated with a proportionally greater loss of lean tissue in older adults. Even in sarcopenic obesity, weight reduction is recommended along with lifestyle interventions focusing on minimizing lean mass loss.[22] Individualized nutritional[5] and physical activity[23–26] strategies should be considered to mitigate the potential risk of excess lean mass loss.[5,11] Nutritional considerations for people receiving OMMs have been reviewed elsewhere and may include, for example, an increase in daily protein intake to 60–75 g/day and up to 1.5 g/kg body weight/day on an individualized basis.[5] In the female and male subgroups, tirzepatide was also consistently associated with significant reductions in measures of adiposity and weight reduction compared with placebo. These results, in combination with the results of analyses by age, suggest that tirzepatide improves overall body composition, with similar proportions of fat mass and lean mass loss compared with placebo.

It is typical that some lean mass is gained with substantial weight gain due to the increased physiomechanical burden on skeletal muscle to carry the extra body weight.[27–29] It is also expected that some degree of lean mass will be lost with substantial weight reduction,[18] which may be mitigated by nutrition[5] and physical activity.[23–26] The present results support the understanding that tirzepatide does not induce disproportionate lean mass loss compared with other established obesity treatment modalities, even with greater total body weight reduction. Other modalities evaluated for proportional body weight reduction include lifestyle changes,[8,30] the OMM semaglutide (a glucagon-like peptide-1 receptor agonist)[31] and bariatric surgery.[32–35]

With respect to lifestyle changes, dietary interventions, including very-low-calorie, low-carbohydrate, low-fat and high-fibre diets, have resulted in proportions of weight reduction similar to those seen in this analysis.[8,30,36] For the OMM semaglutide, the DXA substudy of the STEP 1 trial of adults with obesity or overweight receiving semaglutide reported an absolute reduction of 10.4 kg total fat mass and 6.9 kg total body lean mass, corresponding to a proportional body weight reduction of 60% fat mass and 40% lean mass.[31]

Historically, metabolic and bariatric surgery have induced the greatest amount of body weight reduction, reducing cardiovascular disease and mortality and inducing type 2 diabetes remission and other health benefits.[37,38] A study on the effects of gastric bypass in patients who lost ≥15% of total body weight showed a mean weight reduction of 18.4% (24.6 kg) and a proportion of fat mass loss of 76%.[32] A meta-analysis of different types of metabolic and bariatric surgeries using DXA for body composition showed the proportion of fat mass loss was 55%–86%.[33] Even at higher weight reduction tertiles (>25.9 kg), our results remained comparable with those reported in patients who achieved overlapping degrees of total body weight reduction after bariatric surgery.[34,35] As with other therapeutic interventions for obesity, tirzepatide has demonstrated variable responses among individuals for body weight reduction[13] and body composition. In the clinical setting, the approach for specific high-risk individuals may need to be modified based on treatment response.

4.1 | Limitations

This analysis provided an in-depth evaluation of body composition changes with an OMM by DXA at longer time frames than previous studies and across multiple sites. Whole-body DXA scans, as completed in this substudy, are commonly used in clinical practice and research for body composition.[10] DXA is a valid and highly accepted technique to measure body composition. While the four-compartment model for measuring body composition may be more accurate than DXA alone, it requires additional complex measurements such as whole-body plethysmography and analysis of stable isotope dilution via mass spectrometry that are not amenable to large multisite studies. DXA is also limited in the ability to accommodate patients who exceed length, width and rated load capacity[10,39]; however, the baseline characteristics of this DXA substudy population were comparable with those of the overall population from SURMOUNT-1.[13] Visceral fat from the android region was estimated in this study, not calculated directly, but has a similar relationship to other biomarkers of metabolic health such as visceral fat measured by computed tomography.[39]

The current study provided supportive information for clinical considerations through post hoc analyses of body composition changes during weight reduction with tirzepatide in relevant subgroups. These subgroups included age, sex and weight reduction tertiles. While the results of the subgroup analyses were generally concordant with the overall findings, the subgroups were limited in size. Conclusions based on nominal differences between subgroups should be avoided, and the findings should be interpreted by understanding the limitations associated with post hoc analyses. For example, results were disproportionate in the 50- to <65-year-old placebo group, likely due to the small sample size ($n = 9$). Additionally, an increase in visceral fat but a decrease in waist circumference for the male placebo group ($n = 8$–11) was observed. These are two examples of potential outliers that influence the mean but do not represent typical findings. Furthermore, this analysis did not evaluate physical activity and nutrient intake and their relationship to body composition by DXA. Future research with direct functional outcomes, such as a physical performance battery or the sit-to-stand test, may provide a more translatable outcome to support clinical decision-making.

4.2 | Conclusions

In this DXA substudy of the SURMOUNT-1 trial, tirzepatide resulted in greater total body weight reduction and improved body composition, including fat mass, visceral fat mass and waist circumference reduction than lifestyle alone (placebo). Tirzepatide also reduced fat mass and lean mass in similar proportions to weight loss with placebo, including across subgroup post hoc analyses of age, sex and weight reduction tertiles, leading to improved body composition with clinically meaningful weight reduction. Additionally, previously published data from the overall SURMOUNT-1 study population demonstrated favourable effects of tirzepatide treatment on physical function.

Tirzepatide has demonstrated robust changes in body weight, primarily from reduction in fat mass, with the concomitant proportional loss of lean mass similar to other weight reduction modalities.

AUTHOR CONTRIBUTIONS

The concept and design of the work was by JPD and RG. AS was involved in data acquisition. Analysis of the work was by ML, RFK, DC and CH. All authors were involved in the interpretation of the data. JPD, CH, AS and RG were involved in drafting. All authors provided critical revisions of the manuscript for important intellectual content and approved the manuscript for publication.

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FUNDING INFORMATION

This work was funded by Eli Lilly and Company who was involved in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

CONFLICT OF INTEREST STATEMENT

ML declares payment or honoraria for speaker's bureau and lecture from Eli Lilly and Company and Boehringer Ingelheim as well as advisory board participation with these companies. RFK has received consulting fees from Eli Lilly and Company, Regeneron, Novo Nordisk, Structure, Weight Watchers, Altimmune, Boehringer Ingelheim and Currax, and has participated on a data safety monitoring board or advisory board with Novo Nordisk. JPD, DC, CH, THG, AS and RG are employees and shareholders of Eli Lilly and Company.

DATA AVAILABILITY STATEMENT

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

ETHICS STATEMENT

The overall SURMOUNT-1 (NCT04184622) study and the substudy were conducted in accordance with the principles of the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association and Good Clinical Practice guidelines and were approved by an independent ethics committee or institutional review board at each trial site. All the participants provided written informed consent for the SURMOUNT-1 study and the substudy before participation. Randomization from the overall study applied to the substudy.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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