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ORIGINAL ARTICLE

Effect of tirzepatide on body fat distribution pattern in people with type 2 diabetes

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Abstract

Aims: To describe the overall fat distribution patterns independent of body mass index (BMI) in participants with type 2 diabetes (T2D) in the SURPASS-3 MRI substudy by comparison with sex- and BMI-matched virtual control groups (VCGs) derived from the UK Biobank imaging study at baseline and Week 52.

Methods: For each study participant at baseline and Week 52 ($N = 296$), a VCG of ≥150 participants with the same sex and similar BMI was identified from the UK Biobank imaging study ($N = 40\,172$). Average visceral adipose tissue (VAT), abdominal subcutaneous adipose tissue (aSAT) and liver fat (LF) levels and the observed standard deviations (SDs; standardized normal *z*-scores: *z*-VAT, *z*-aSAT and *z*-LF) were calculated based on the matched VCGs. Differences in *z*-scores between baseline and Week 52 were calculated to describe potential shifts in fat distribution pattern independent of weight change.

Results: Baseline fat distribution patterns were similar across pooled tirzepatide (5, 10 and 15 mg) and insulin degludec (IDeg) arms. Compared with matched VCGs, SURPASS-3 participants had higher baseline VAT (mean [SD] *z*-VAT +0.42 [1.23]; $p < 0.001$) and LF (*z*-LF +1.24 [0.92]; $p < 0.001$) but similar aSAT (*z*-aSAT −0.13 [1.11]; $p = 0.083$). Tirzepatide-treated participants had significant decreases in *z*-VAT (−0.18 [0.58]; $p < 0.001$) and *z*-LF (−0.54 [0.84]; $p < 0.001$) but increased *z*-aSAT (+0.11 [0.50]; $p = 0.012$). Participants treated with IDeg had a significant change in *z*-LF only (−0.46 [0.90]; $p = 0.001$), while no significant changes were observed for *z*-VAT (+0.13 [0.52]; $p = 0.096$) and *z*-aSAT (+0.09 [0.61]; $p = 0.303$).

Conclusion: In this exploratory analysis, treatment with tirzepatide in people with T2D resulted in a significant reduction of *z*-VAT and *z*-LF, while *z*-aSAT was increased from an initially negative value, suggesting a possible treatment-related shift towards a more balanced fat distribution pattern with prominent VAT and LF loss.

KEYWORDS
abdominal subcutaneous adipose tissue, fat distribution pattern, liver fat, Tirzepatide, visceral adipose tissue

1 | INTRODUCTION

There is a strong link between obesity and type 2 diabetes (T2D) as obesity is a leading risk factor for T2D[1] and people with obesity are ~10 times more likely to develop T2D.[2] However, there is substantial heterogeneity within obesity, with people at both high and low risk of developing cardiometabolic disease.[3] Previous research shows that different patterns of body fat distribution (visceral fat, subcutaneous fat, and liver fat [LF]) are linked to separate cardiometabolic risk profiles and could be used to identify clinically meaningful subphenotypes within obesity.[4,5] People with obesity in whom fat is stored predominantly as visceral rather than subcutaneous fat are at a higher risk of developing cardiometabolic disease and related complications.[6–8] In addition, recent research from the Dallas Heart Study and UK Biobank study cohorts further indicates that the balance between visceral fat and LF is of high importance: in the presence of visceral obesity, high LF was linked to T2D incidence while low LF was linked most strongly to cardiovascular disease (CVD) incidence.[4,9]

Response to weight loss interventions varies greatly, both within and across treatment strategies.[10] However, concurrent loss of visceral fat, subcutaneous fat and LF is commonly observed during successful weight loss.[11–13] Yet, when a reduction in, for example, visceral fat is observed during weight loss, it is challenging to determine whether that loss was in line with the weight change, smaller than expected for the weight loss, or greater than expected (indicating a targeted effect on visceral fat beyond that expected for the weight lost). The use of body fat *z*-scores allows a person's specific body fat distribution phenotype to be described independently of their sex and body size (height, weight, and body mass index [BMI]), indicating whether a person has more or less of, for example, visceral fat than would expected for their BMI.[14] A weight-invariant way of describing the body fat distribution phenotype is especially important as the options for weight management are growing. In a landscape where a multitude of treatments achieve significant weight loss but to varying degrees, sex- and BMI-invariant body fat *z*-scores can help indicate whether there has been a shift in fat distribution pattern and whether a certain treatment may have a targeted effect on a single (or multiple) fat depot(s) beyond body weight loss per se.

Body weight management is a major part of the holistic approach to diabetes management in the recent consensus report by the American Diabetes Association and European Association for the Study of Diabetes.[15] Indeed, body weight reduction has been shown to improve glycated haemoglobin (HbA1c) levels and reduce the risk of obesity-related complications. Incretin-based therapies such as glucagon-like peptide-1 receptor agonists (GLP-1RAs) and tirzepatide, a novel glucose-dependent insulinotropic polypeptide and GLP-1RA, have shown high efficacy for weight management among patients with T2D, including by reducing food intake through direct action in the central nervous system.[16] However, it is unclear whether or not GLP-1RAs and tirzepatide can specifically impact the distribution of fat mass beyond that seen with overall weight loss.

In a substudy of the SURPASS-3 trial, a randomized controlled trial comparing once-weekly tirzepatide (5, 10 and 15 mg) with once-daily basal insulin degludec in patients with T2D, magnetic resonance imaging (MRI) was used to measure participants' visceral fat, subcutaneous fat, and LF.[17] While LF was reduced with both treatments at the Week 52 primary endpoint (mean [standard error] of −8.09% [0.57] with pooled tirzepatide 10 and 15 mg vs. −3.38% [0.83] with insulin degludec),[11] a mean overall weight loss of −9.6 kg with concurrent visceral and subcutaneous fat reductions occurred with tirzepatide, and a mean overall weight gain of +3.2 kg with concurrent visceral and subcutaneous fat increases occurred with insulin degludec (data on file).

The aim of this work was to further describe baseline and potential shifts in body fat distribution patterns independent of BMI and weight change in the SURPASS-3 MRI substudy by using the body fat *z*-score method.

2 | METHODS

2.1 | Study design and participants

2.1.1 | SURPASS-3 MRI substudy

The study design of the SURPASS-3 study and SURPASS-3 MRI substudy (ClinicalTrials.gov identifier: NCT03882970) were previously published and described in detail.[11,16] In the SURPASS3 study, insulin-naïve adults with T2D who had an HbA1c concentration of 53–91 mmol/mol (7.0%–10.5%), a BMI of ≥25 kg/m^2, and stable weight at baseline and were receiving metformin with or without a sodium-glucose cotransporter-2 inhibitor were randomly assigned (1:1:1:1) to receive a once-weekly subcutaneous injection of tirzepatide (5, 10 or

15 mg) or a once-daily subcutaneous injection of titrated insulin degludec. Tirzepatide was first given at a dose of 2.5 mg, which was escalated by 2.5 mg every 4 weeks until the assigned dose was reached.[18] Additional specific exclusion criteria for the SURPASS-3 MRI substudy were a fatty liver index value <60 (to include patients with probable hepatic steatosis), contraindications to an MRI scan (such as the use of cardiac pacemakers and metal implants), claustrophobia precluding completion of an MRI scan, history of excessive alcohol intake (males: >21 units/week; females: >14 units/week), and a BMI >45 kg/m^2.[11]

In this exploratory analysis, which excluded participants that did not have both baseline and Week 52 data available, tirzepatide doses were pooled (5, 10 and 15 mg, $N = 190$) and compared with insulin degludec ($N = 56$).

2.1.2 | UK Biobank imaging study

This analysis also included data from the 40 172 participants who underwent a first scan in the UK Biobank imaging study. UK Biobank is a long-term study following 500 000 volunteers aged 40–69 years who were recruited from 2006 to 2010. As a substudy, 100 000 participants are being recalled for a detailed imaging assessment, including a repeat baseline assessment.[19] The UK Biobank data were used to stratify matched virtual control groups and calculate body fat *z*-scores among the SURPASS-3 MRI substudy participants. Demographics and characteristics for the UK Biobank study population are shown in Table S1.

The UK Biobank study data were accessed under project ID 6569. The study was approved by the North-West Multicentre Research Ethics Committee, UK. Written informed consent was obtained before study entry.

2.1.3 | MRI measurements

Both SURPASS-3 MRI and UK Biobank participants underwent imaging using a rapid (6–10-min) protocol in 1.5- or 3-T MRI scanners (manufactured by Siemens Healthineers, Erlangen, Germany; Philips, Amsterdam, Netherlands; or General Electric, Chicago, IL, USA).[4,17] SURPASS-3 MRI participants were imaged using the same scanner and imaging-acquisition parameters used for both time points.[17] Neck-to-knee images from both the SURPASS-3 MRI and UK Biobank studies were analysed for quantification of visceral adipose tissue (VAT) volume and abdominal subcutaneous adipose tissue (aSAT) volume using AMRA Researcher (AMRA Medical AB, Linköping, Sweden). Briefly, the process involves: (1) calibration of images using fat-referenced MRI; (2) generation of automatic segmentations using registration of atlases with ground truth labels for fat compartments; (3) quality control of the automatic segmentation by two trained and independent operators with anatomical knowledge and the possibility to assess potential image quality issues as well as adjust the segmentation, if needed; and (4) quantification of fat volumes in segmented regions. Liver images were analysed for liver proton density fat fraction (LF) by AMRA Researcher (UK Biobank participants) or BioTel Research (Cardiocore and VirtualScopics, Rochester, New York, NY, USA; SURPASS-3 MRI substudy participants). The reproducibility and repeatability of body composition analysis across the protocols, manufacturers and field strengths used in this study were high, allowing for cross-study comparison without application of correction factors.[4,20]

We defined VAT as adipose tissue within the abdominal cavity, excluding adipose tissue outside the abdominal skeletal muscles and adipose tissue and lipids within the cavity and posterior of the spine and back muscles. aSAT was defined as subcutaneous adipose tissue in the abdomen from the top of the femoral head to the top of the T9 thoracic vertebra. LF was defined as the average proton density fat fraction across nine user-defined regions of interest.

2.2 | Statistical analysis

2.2.1 | Calculation of body fat *z*-scores

A virtual control group, comprising at least 150 sex- and BMI-matched participants from the UK Biobank study, was stratified for each participant and time point.[14] Each participant's body fat *z*-scores (aSAT *z*-score [*z*-aSAT], VAT *z*-score [*z*-VAT] and LF *z*-score [*z*-LF]) were calculated as the number of standard deviations (SDs) between the participant value and the average value of their sex- and BMI-matched virtual controls (Figure 1). Details can be found in the Supplementary Material.

A body fat *z*-score (e.g., *z*-VAT) of 0 means that a participant carried the exact same amount as the average value of their sex- and BMI-matched virtual controls, while a negative/positive body fat *z*-score indicated that they carried less/more than the average value of their sex- and BMI-matched virtual controls.

2.2.2 | Body fat distribution patterns in the SURPASS-3 MRI substudy

To determine whether participants at baseline had stored more, less, or similar VAT, aSAT and LF than/to the average for their sex and BMI, each body fat *z*-score distribution was tested towards 0 using a standard *t*-test. To determine whether the body fat distribution pattern was significantly different following treatment with tirzepatide and/or insulin degludec, baseline *z*-scores were compared to corresponding Week 52 *z*-scores using a paired *t*-test. In addition, the deviation in litres (VAT and aSAT) and percentage points (LF) between the participants and the average value of their sex- and BMI-matched virtual controls at baseline were compared to corresponding deviations at Week 52 using a paired *t*-test.

To compare potential changes in fat distribution pattern between tirzepatide and insulin degludec, differences in changes of body fat *z*-scores were tested using a standard *t*-test.

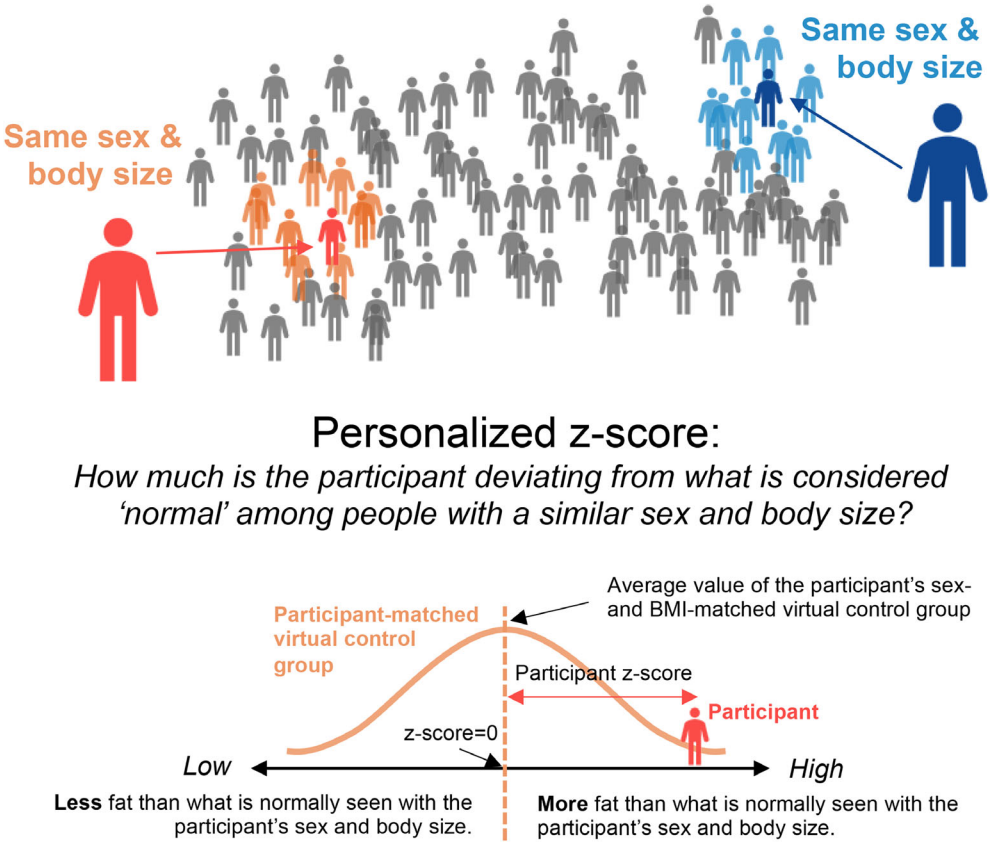

FIGURE 1 Illustration of the body fat *z*-score calculation. BMI, body mass index.

As the participants in the SURPASS-3 MRI substudy were generally younger than the UK Biobank study participants, the effect of age on the body fat *z*-scores was estimated using a linear regression model and was subsequently used to calculate age-adjusted body fat *z*-scores. In all analyses, both unadjusted and age-adjusted *z*-scores were evaluated. Details can be found in the Supplementary Material.

3 | RESULTS

Among participants included in the SURPASS-3 MRI substudy, 42% were female. Participants had an overall mean age of 56 years, a mean diabetes duration of 8 years, a mean HbA1c of 65.8 mmol (8.2%), and a mean BMI of 33.5 kg/m^2. The overall mean baseline LF content was 15.7% among participants, while mean aSAT and VAT volumes were 10.4 L and 6.6 L, respectively.[11] Participants showed a fat distribution pattern characterized by higher baseline VAT (mean [SD] VAT 0.27 [1.78] L, *z*-VAT 0.42 [1.23], age-adjusted *z*-VAT 0.66 [1.12]) and LF (mean [SD] 8.36% [8.69%], *z*-LF 1.24 [0.92], age-adjusted *z*-LF 1.32 [0.95]) than that observed for sex- and BMI-matched virtual controls from the UK Biobank study. Mean (SD) aSAT was lower (−0.46 [2.10] L, *z*-aSAT −0.13 [1.11], age-adjusted *z*-aSAT −0.08 [1.12]) at baseline than that observed for sex- and BMI-matched virtual controls from the UK Biobank study. Magnitudes of fat *z*-scores were similar across tirzepatide and insulin degludec arms at baseline. Table 1 summarizes the demographics and characteristics of participants in the tirzepatide and insulin degludec arms with both baseline and Week 52 data. Overall study population characteristics were previously published in detail.[17]

For tirzepatide, positive significant correlations were observed between change in fat depots and body weight change (Figure 2A–C). In addition, significant but weaker correlations were observed between changes in the different fat depots (Figure 2D–F). Correlations were similar comparing tirzepatide to insulin degludec except for change in LF, which was not significantly correlated with weight change or aSAT change with insulin degludec. Corresponding results for body fat *z*-score changes within tirzepatide showed weaker correlations with weight change and variable *z*-score changes at any given weight change (Figure S1).

Results from the comparison of baseline to Week 52 data showed, in addition to the weight change, significant differences in body fat distribution patterns (Figure 3). Among participants treated with insulin degludec, who experienced an overall mean weight gain of +3.2 kg, a significant decrease in *z*-LF was observed (mean [SD] −0.46 [0.90]; $p = 0.001$), while VAT and aSAT increased, resulting in nonsignificant increases in *z*-VAT (mean [SD] +0.13 [0.52]; $p = 0.096$) and *z*-aSAT (mean [SD] +0.09 [0.61]; $p = 0.303$). Among participants treated with tirzepatide who experienced an overall mean weight loss of −9.6 kg, significant decreases in *z*-LF (mean [SD] −0.54 [0.84]; $p < 0.001$) and *z*-VAT (mean [SD] −0.18 [0.58]; $p < 0.001$) were observed, with an increase in *z*-aSAT (mean [SD] +0.11 [0.50]; $p = 0.012$).

TABLE 1 Demographics and characteristics of the SURPASS-3 MRI substudy population.

	Pooled tirzepatide ($N = 190$)			Insulin degludec ($N = 56$)		
	Baseline	Week 52	*p* value	Baseline	Week 52	*p* value
Age, years	56.0 (9.8)	57.0 (9.8)		56.1 (10.2)	57.1 (10.2)	
Male sex, *n* (%)	116 (61.1)	116 (61.1)		31 (55.4)	31 (55.4)	
Duration of diabetes, years	9.0 (7.3)	10.0 (7.3)		6.8 (4.8)	7.8 (4.8)	
HbA1c, mmol/mol	67.3 (9.8)	42.8 (9.9)	<0.001	65.8 (11.9)	53.0 (12.1)	<0.001
HbA1c, %	8.3 (0.9)	6.1 (0.9)	<0.001	8.2 (1.1)	7.0 (1.1)	<0.001
BMI, kg/m^2	33.7 (4.8)	30.3 (5.0)	<0.001	32.7 (4.5)	33.8 (5.5)	<0.001
Weight, kg	95.8 (16.5)	86.3 (16.9)	<0.001	90.7 (16.2)	93.9 (19.1)	<0.001
Waist circumference, cm	111.2 (11.4)	102.7 (12.5)	<0.001	108.9 (11.5)	111.2 (12.5)	0.007
LF content, %	16.1 (8.5)	8.8 (6.1)	<0.001	17.0 (10.4)	13.5 (8.4)	0.008
VAT volume, L	6.7 (2.0)	5.3 (2.1)	<0.001	6.0 (1.8)	6.5 (2.0)	0.003
aSAT volume, L	10.7 (4.1)	8.7 (3.8)	<0.001	9.8 (4.1)	10.5 (4.3)	<0.001
VAT percentage of total abdominal fat, %	40.0 (11.1)	38.5 (11.1)	<0.001	39.5 (10.5)	39.5 (10.7)	0.978
Fatty liver index	85.7 (13.0)	64.5 (26.2)	<0.001	81.3 (17.2)	81.8 (18.3)	0.693

Note: Data are shown as mean (standard deviation) unless otherwise indicated. Pooled tirzepatide includes 5, 10 and 15 mg doses. *p* values are from paired *t*-tests comparing baseline to Week 52 values.
Abbreviations: aSAT, abdominal subcutaneous adipose tissue; BMI, body mass index; HbA1c, glycated haemoglobin; LF, liver fat; *N*, population size; *n*, sample size; VAT, visceral adipose tissue.

Overall, the direction of change in body fat distribution pattern with tirzepatide was towards that of their sex- and BMI-matched virtual controls. At Week 52, participants treated with tirzepatide had more similar amounts of both VAT (mean [SD] 0.00 [1.74] L, *z*-VAT 0.22 [1.32]), aSAT (−0.17 [1.92] L, *z*-aSAT 0.01 [1.14]), and LF (2.56 [5.26] percentage points, *z*-LF 0.67 [0.92]) as compared to their sex- and BMI-matched virtual controls. Following treatment with insulin degludec, the only fat depot that had a magnitude significantly closer to the sex- and BMI-matched virtual controls was LF (5.87 [8.54] percentage points; *z*-LF 0.92 [1.21] SD), while deviations from the sex- and BMI-matched virtual controls at Week 52 in VAT (0.37 [1.77] L, *z*-VAT 0.51 [1.1] SD) and aSAT (−0.45 [2.45] L, *z*-aSAT −0.06 [1.27] SD) were similar compared to baseline. Full details can be found in Table S2. The age-adjusted analysis showed similar results; full results are shown in Table S3.

4 | DISCUSSION

To our knowledge, this is the first study to assess shifts in body fat distribution in response to pharmacological treatment using weight-invariant body fat *z*-scores. In this exploratory analysis, tirzepatide treatment was associated with a significant decrease in both *z*-VAT and *z*-LF, suggesting a potential targeted effect on VAT and LF. While *z*-VAT and *z*-LF were reduced, an increase in *z*-aSAT was observed, indicating the participants lost less aSAT than described by the weight loss. Taken together, all fat *z*-scores moved towards 0 (*z*-VAT and *z*-LF decreased from positive values and *z*-aSAT increased from a negative value) resulting in a shift towards a more balanced body fat distribution pattern. In contrast, basal insulin degludec treatment significantly decreased *z*-LF only, with no specific impact on *z*-VAT or *z*-aSAT.

Beyond improved glycaemic control, this shift in the fat distribution pattern with tirzepatide treatment was accompanied by a decrease in triglycerides and very-low-density lipoprotein cholesterol concentrations and a significant increase in high-density lipoprotein cholesterol concentration.[11] The overall weight loss accompanied by a beneficial shift in the fat distribution pattern and several cardiometabolic risk parameters provides more evidence that tirzepatide can be an effective treatment for obesity. The results of the SURMOUNT 1–4 clinical trials support this notion and confirmed the beneficial effect of tirzepatide in chronic weight management, as well as the improvement on multiple cardiometabolic risk markers.[21–24]

Absolute change or percent change in body weight and/or BMI are still typical endpoints in clinical trials evaluating treatments for obesity and related disorders. However, the results from this study clearly illustrate that pharmacological treatments for T2D can alter the fat distribution pattern in various ways, independent of weight change, making fat distribution profiling an attractive and modifiable endpoint for future trials in obesity therapy, which is a fast-growing field of research.[25] As the balance between different fat depots is strongly linked to an individual's cardiometabolic risk profile, it is important to target not only one single fat depot alone but also the overall pattern (similar to targeting an overall dietary pattern rather than a single macronutrient or food type). In recent years, increasing emphasis has been placed on the development of pharmacological treatments for nonalcoholic fatty liver disease. Although the target is treatment of nonalcoholic steatohepatitis and/or fibrosis, reduction of LF has been used as an endpoint in several trials.[26] Developing knowledge of potential shifts in overall fat distribution patterns as a result

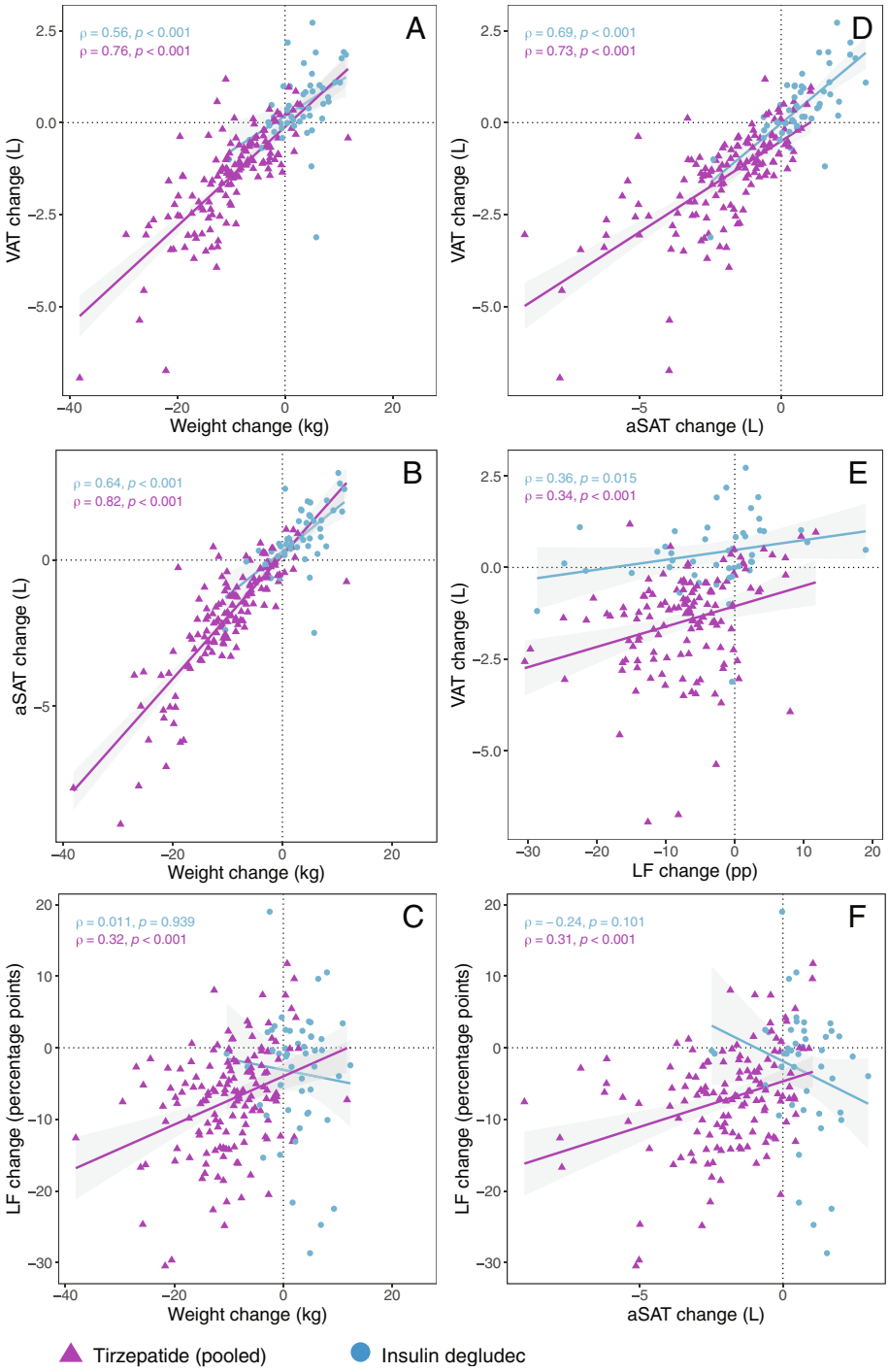

FIGURE 2 Correlations between absolute changes in each fat depot and weight change. aSAT, abdominal subcutaneous adipose tissue; LF, liver fat; pp, percentage points; VAT, visceral adipose tissue.

of pharmacological treatments in this area is important, especially when a significant reduction in LF occurs in study participants with stable body weight or in parallel with weight gain, as is the case for glitazones for example.[27] In the present study, it should also be noted that both tirzepatide and degludec reduced hepatic fat content, but by different mechanisms (as illustrated in Figure 2C). Whereas tirzepatide appears to act primarily via an overall reduction in body weight and food intake, the action of insulin degludec to reduce LF is probably mediated by a decrease in lipolysis, as previously reported with insulin therapy.[28,29]

While robust evidence shows VAT is an independent risk factor for cardiovascular and metabolic morbidity and mortality,[30] subcutaneous fat has been given less attention, probably because subcutaneous fat alone has shown only a weak association (or none) with incident metabolic disease depending on the population studied.[6–8] However, a skewed fat distribution pattern between VAT and aSAT (*z*-aSAT <0 and *z*-VAT >0) has been linked to a higher risk of both incident CVD and T2D compared with a balanced fat distribution pattern between VAT and aSAT, still with excessive amounts of both fats in relation to BMI (*z*-aSAT >0 and *z*-VAT >0).[14] Findings from

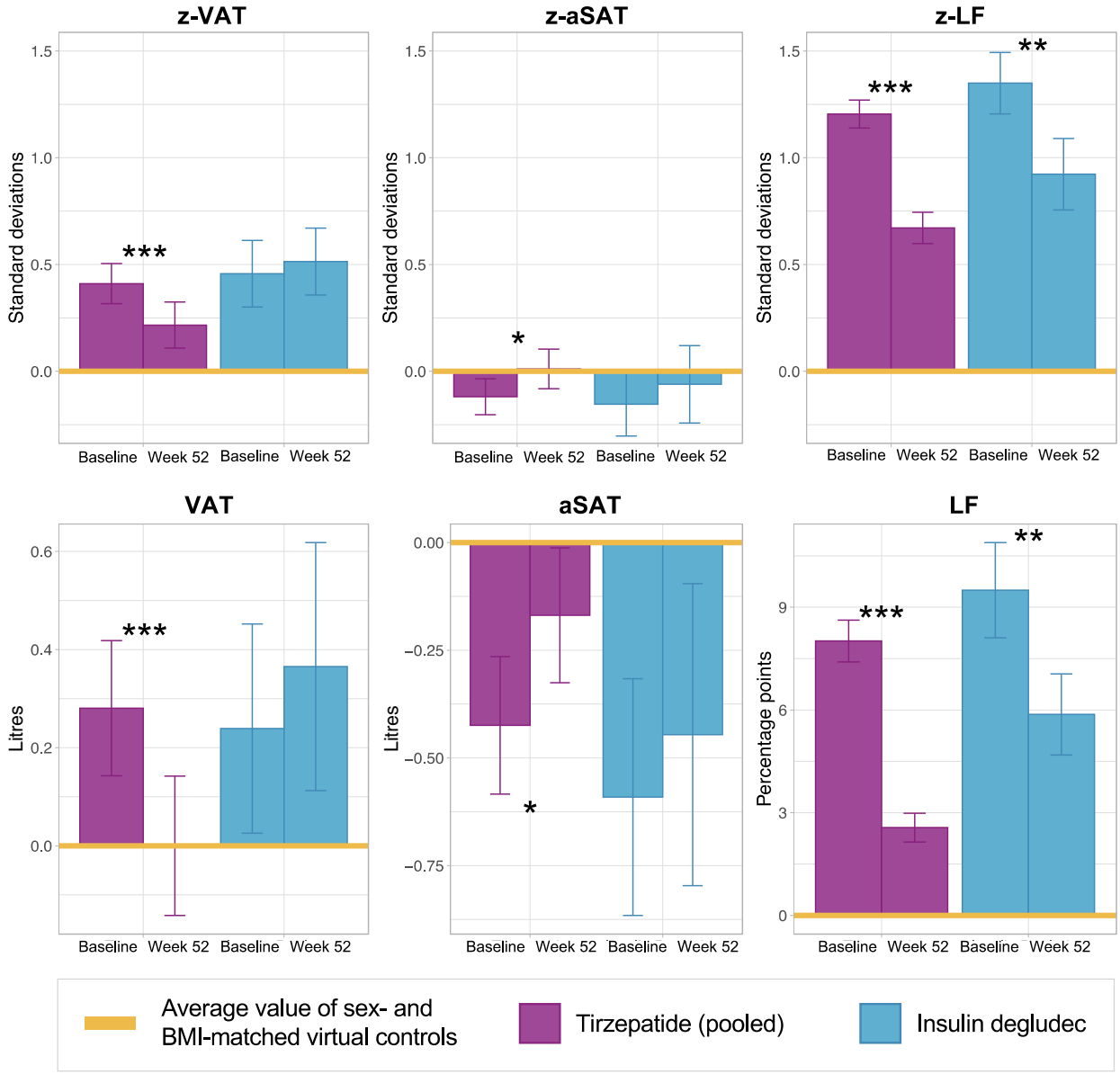

FIGURE 3 Differences in body fat distribution pattern comparing baseline and Week 52 data following treatment with tirzepatide and insulin degludec expressed as deviations from sex- and body mass index (BMI)-matched virtual controls in *z*-scores (top row) and in litres (visceral adipose tissue [VAT] and abdominal subcutaneous adipose tissue [aSAT]) and percentage points (liver fat [LF]; bottom row). Bars indicate group means with standard error of the mean. Statistical significance of differences between baseline and Week 52 data according to a paired *t*-test is indicated by asterisks: no asterisk = nonsignificant; **p* < 0.05; ***p* < 0.01; ****p* < 0.001. Sex- and BMI-matched virtual controls were stratified from the UK Biobank imaging study. *z*-aSAT, abdominal subcutaneous adipose tissue *z*-score; *z*-LF; liver fat *z*-score; *z*-VAT, visceral adipose tissue *z*-score.

this study show that *z*-aSAT can be modulated by pharmacological treatment. Participants included in the SURPASS-3 MRI substudy had less aSAT than their sex- and BMI-matched virtual controls (negative *z*-aSAT) at baseline, which is in line with what was found for participants with T2D in the UK Biobank study, potentially indicating a decreased ability to store subcutaneous fat.[14] After treatment with tirzepatide, *z*-aSAT significantly increased from negative to a value near 0, indicating a potential preservation of aSAT in relation to the weight lost with tirzepatide. The question remains of whether or not these shifts in body fat distribution patterns result in changes in adipose tissue function. Results from a separate SURPASS-3 MRI substudy data analysis showed that changes in VAT and aSAT were accompanied by improvements in several markers such as adiponectin, leptin, adiponectin/leptin, or adipose tissue insulin resistance, which would indicate a beneficial effect on adipose tissue functionality.[11] In this context, it should also be noted that tirzepatide has been shown to decrease several inflammatory biomarkers, such as high-sensitivity C-reactive protein and intercellular adhesion molecule-1,[31] that have been associated with cardiovascular risk related to obesity.[32]

This analysis has several limitations, and the exploratory results presented should be interpreted with caution. The SURPASS-3 MRI substudy and UK Biobank imaging study were conducted as two separate studies, and some baseline demographics and characteristics differed between cohorts. Although the mean (SD) aSAT and VAT values in relation to BMI in the SURPASS-3 MRI substudy were similar to those observed for participants with T2D in the UK Biobank study (*z*-aSAT −0.08 [1.12], age-adjusted, vs. −0.02 [0.98] in UK Biobank; *z*-VAT 0.66 [1.12], age-adjusted, vs. 0.49 [1.11] in UK Biobank), participants in the SURPASS-3 MRI substudy showed higher mean (SD) LF, both in relation to their BMI and in comparison to participants with T2D in the UK Biobank study (*z*-LF 1.32 [0.95], age-adjusted, vs. 0.53 [1.13] in UK Biobank). Although participants with T2D in the UK Biobank study were generally older than those in the SURPASS-3 MRI substudy, the skewed fat distribution pattern observed is probably a result of the inclusion criteria for the SURPASS-3 MRI substudy (especially the fatty liver index of >60 to include patients with liver steatosis) rather than because of age differences. Further studies are needed to determine whether a similar, beneficial shift in body fat distribution would occur in patients with T2D who have less LF accumulated and/or in a patient population with obesity but without T2D. The age difference between participants in the SURPASS-3 MRI substudy and the UK Biobank study did not allow for matching on age when stratifying matched controls to calculate the body fat *z*-scores. However, the effects of age on body fat *z*-scores, estimated using data from UK Biobank, were used to adjust *z*-scores in the SURPASS-3 MRI substudy. The age difference between cohorts affected the baseline values for body fat *z*-scores but not the interpretation of change in *z*-scores (as everyone was approximately 1 year older at Week 52) or differences between treatment arms (as there was no significant difference in age between treatment arms).[11] There were no available data on food intake or physical activity in SURPASS-3 MRI study, and therefore we cannot assess if any differences between treatment groups could have influenced the results presented in this analysis.

In addition, the study did not compare tirzepatide directly with a GLP-1RA alone for assessing potential differences in the observed effects on fat distribution patterns. It would also be of interest to compare tirzepatide to an alternative treatment achieving comparable weight loss. However, such studies are not available and reporting the effect of tirzepatide on fat distribution using virtual control groups will allow future, separate comparisons with other T2D and/or obesity treatments using the same method. Lastly, this study calculated body fat *z*-scores for each SURPASS-3 MRI participant based on people with the same sex and BMI to describe their fat distribution phenotype independent of their BMI. The body fat *z*-scores at baseline were then compared to those at Week 52 to assess whether there had been a shift in fat distribution pattern during treatment independent of the weight change observed. The concept is similar to how bone mineral density *z*-scores are calculated for osteoporosis assessment and follow-up, where the patient is compared to people with the same sex and age. Previous studies have shown that the body fat *z*-scores are highly weight-invariant, both in general population and within obesity class I and II (BMI 30–40 kg/m^2) specifically, indicating that comparisons of changes in fat *z*-scores can be made between individuals and groups with different magnitudes of weight loss.[14,33] However, this is a novel concept to assess fat distribution pattern and further research is needed to understand the common effects on body fat distribution patterns across different weight loss interventions.

A more balanced body fat distribution pattern (with *z*-scores close to 0) is associated with low prevalence of disease, also in people with overweight.[14] Recent research investigating the implications between VAT and LF imbalances has shown that low LF in the presence of visceral obesity is strongly associated with incident CVD, raising the question of whether LF reduction as a response to pharmacological treatment without a concomitant reduction in VAT could lead to higher CVD risk.[5,9] In the SURPASS-3 MRI substudy, treatment with insulin degludec showed a significant reduction of LF and *z*-LF, while *z*-VAT remained constant. It is unknown if continued treatment with insulin degludec would lead to a further shift in the balance between VAT and LF and if such a change could be associated with higher CVD risk. Instead, tirzepatide showed a decrease in LF and *z*-LF along with a reduction in VAT and *z*-VAT, and an increase in *z*-aSAT. Taken together, this might indicate a shift towards a more beneficial fat distribution pattern independent of weight change.

In conclusion, in this exploratory analysis of patients with T2D, treatment with tirzepatide, and not insulin degludec, resulted in a significant reduction of both *z*-VAT and *z*-LF. This result suggests a potentially more beneficial shift in fat distribution pattern with tirzepatide than with insulin.

AUTHOR CONTRIBUTIONS

Jennifer Linge contributed to the conception of the work. Ángel Rodríguez and Jennifer Linge were involved in the design of the work. Ross Bray was involved in the acquisition of the data. The analysis was carried out by Jennifer Linge, Mikael Petersson and Ross Bray. Ángel Rodríguez, Bertrand Cariou, Ian Neeland, Jennifer Linge, Laura Fernández Landó, Mikael Petersson, Ross Bray and Olof Dahlqvist Leinhard interpreted the data. Jennifer Linge and Bertrand Cariou wrote the first draft, and all authors critically revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

Bertrand Cariou reports grants and personal fees from Amgen, Regeneron, and Sanofi and personal fees from Abbott, AstraZeneca, Bristol Myers Squibb, Eli Lilly and Company, LVL Médical/Air Liquide,

Novartis, Novo Nordisk, Regeneron and Sanofi. Jennifer Linge, Olof Dahlqvist Leinhard and Mikael Petersson are employees of AMRA Medical AB, Sweden. Ian Neeland has received consulting and speaking honoraria from Boehringer Ingelheim/Eli Lilly Alliance, Bayer Pharmaceuticals and Nestlé Health Sciences. Laura Fernández Landó, Ross Bray and Ángel Rodríguez are employees and shareholders of Eli Lilly and Company.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15566.

DATA AVAILABILITY STATEMENT

Lilly 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.

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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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