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Tirzepatide Treatment and Associated Changes in β-Cell Function and Insulin Sensitivity in People With Obesity or Overweight With Prediabetes or Normoglycemia: A Post Hoc Analysis From the SURMOUNT-1 Trial

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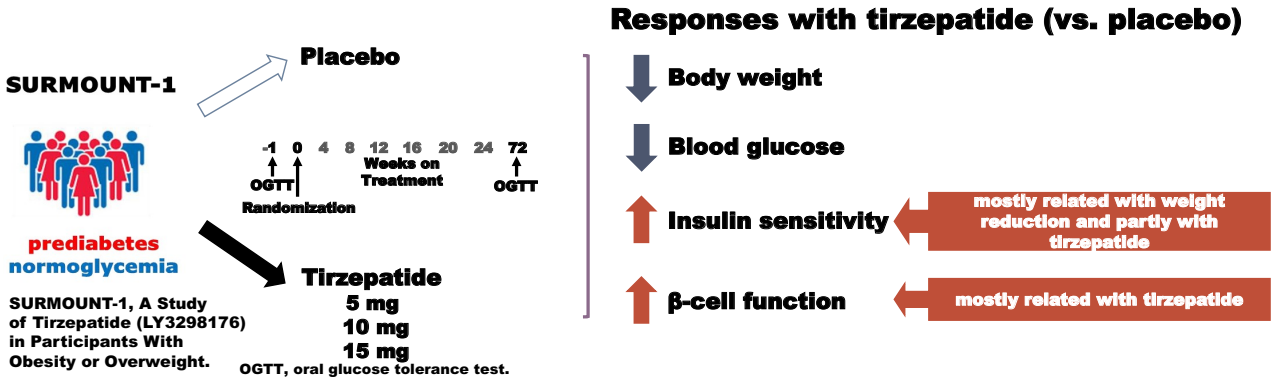
Objective: to assess insulin sensitivity and β-cell function in adults with obesity or overweight (BMI ≥ 27 kg/m²) and with either prediabetes or normoglycemia at baseline treated with tirzepatide for 72 weeks (post hoc analysis from SURMOUNT-1 trial)



All responses were observed in participants with prediabetes and with normoglycemia.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  The possible effect of tirzepatide on β-cell function and insulin sensitivity in people with obesity/overweight, but without type 2 diabetes, deserves investigation.
- **What is the specific question we wanted to answer?**
  We investigated whether tirzepatide treatment was associated with improved insulin sensitivity and β-cell function in adults with prediabetes or normoglycemia and obesity/overweight.
- **What did we find?**
  Tirzepatide treatment was associated with improved insulin sensitivity (strongly related to decreased body weight and partially related to tirzepatide treatment) and β-cell function (strongly associated with tirzepatide treatment) in this population, irrespective of glycemic status.
- **What are the implications of our findings?**
  Tirzepatide may prevent or delay the onset of type 2 diabetes in adults with obesity/overweight through enhancing both β-cell function and insulin sensitivity.

Tirzepatide Treatment and Associated Changes in β-Cell Function and Insulin Sensitivity in People With Obesity or Overweight With Prediabetes or Normoglycemia: A Post Hoc Analysis From the SURMOUNT-1 Trial

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BRIEF REPORT

OBJECTIVE

We assessed insulin sensitivity and β-cell function in adults with obesity/overweight, without diabetes, treated with tirzepatide for 72 weeks.

RESEARCH DESIGN AND METHODS

This post hoc analysis from the Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight (SURMOUNT-1) trial investigated tirzepatide versus placebo in 2,539 participants with BMI ≥27 kg/m^2 and either prediabetes or normoglycemia at baseline. Model-derived parameters of β-cell function and insulin sensitivity were assessed from oral glucose tolerance tests.

RESULTS

At week 72, tirzepatide treatment was associated with body weight reduction and improvements in insulin sensitivity and β-cell function measures overall and in participants with prediabetes or normoglycemia. In multivariate regression models, improvements in insulin sensitivity were associated mostly with weight reduction and partly with tirzepatide treatment, whereas enhancement in β-cell function was mostly associated with tirzepatide treatment.

CONCLUSIONS

In adults with obesity/overweight without type 2 diabetes, tirzepatide treatment was associated with improved β-cell function and insulin sensitivity, partly independent of weight reduction.

In the Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight (SURMOUNT-1) clinical trial involving adults with obesity or overweight without diabetes, 72 weeks of treatment with tirzepatide, a long-acting glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor agonist (RA), was associated with substantial body weight reduction, >20% in the highest dose group (1). In adults with type 2 diabetes, beneficial associations between tirzepatide and β-cell function and insulin sensitivity have been shown (2–4). However, data on these effects in

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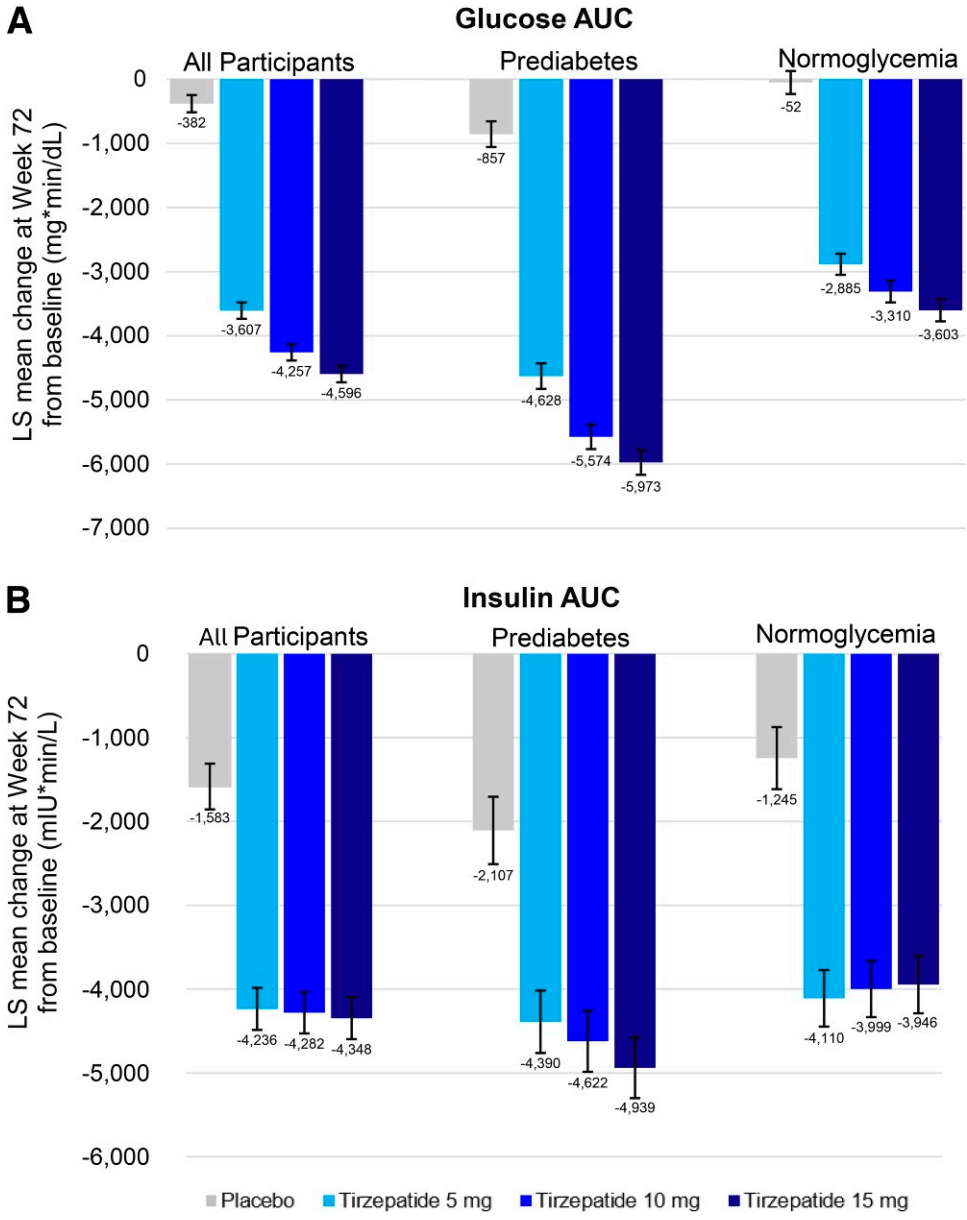

Figure 1—Changes in glucose AUC (*A*) and insulin AUC (*B*) at week 72 from baseline for the overall SURMOUNT-1 study population and by glycemic status at baseline. Data are least-squares (LS) mean ± SE. For both outcomes, changes were significantly greater with tirzepatide compared with placebo, irrespective of glycemic status ($P < 0.001$).

people with obesity without diabetes are limited. This post hoc analysis of SURMOUNT-1 participants examined changes in insulin sensitivity and β-cell function with tirzepatide and their relation to body weight changes.

RESEARCH DESIGN AND METHODS

Study Population and Design

In the SURMOUNT-1 trial, adult participants (n = 2,539) with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with one or more weight-related comorbidity, excluding diabetes, were randomized (1:1:1:1) to once-weekly tirzepatide (5, 10, or 15 mg) or placebo for 72 weeks, in conjunction with lifestyle modification (1). Glycated hemoglobin (HbA_{1c}) and fasting serum glucose and insulin were measured at baseline and weeks 12, 24, 36, 48, 60, and 72 of treatment. A 75-g oral glucose tolerance test (OGTT) was administered at baseline and week 72, with measurements of glucose, insulin, and C-peptide concentrations (0, 30, 60, 90, and 120 min). Participants' baseline glycemic status (i.e., prediabetes or normoglycemia) was assessed using standard criteria (5).

β-Cell Function and Insulin Sensitivity

β-Cell function was assessed using a validated model of insulin secretion during the OGTT (6,7). Main β-cell function parameters were *1*) insulin secretion rate (ISR); *2*) β-cell glucose sensitivity (β-GS); *3*) ISR at a fixed glucose concentration of 5.4 mmol/L ($ISR_{5.4\ mmol/L}$); *4*) total insulin secretion during the OGTT; *5*) potentiation of ISR; and *6*) β-cell rate sensitivity (β-RS). The 30-min insulinogenic index (IGI) and the area under the curve (AUC) for glucose, insulin, and C-peptide concentrations during the OGTT were also calculated. Insulin sensitivity

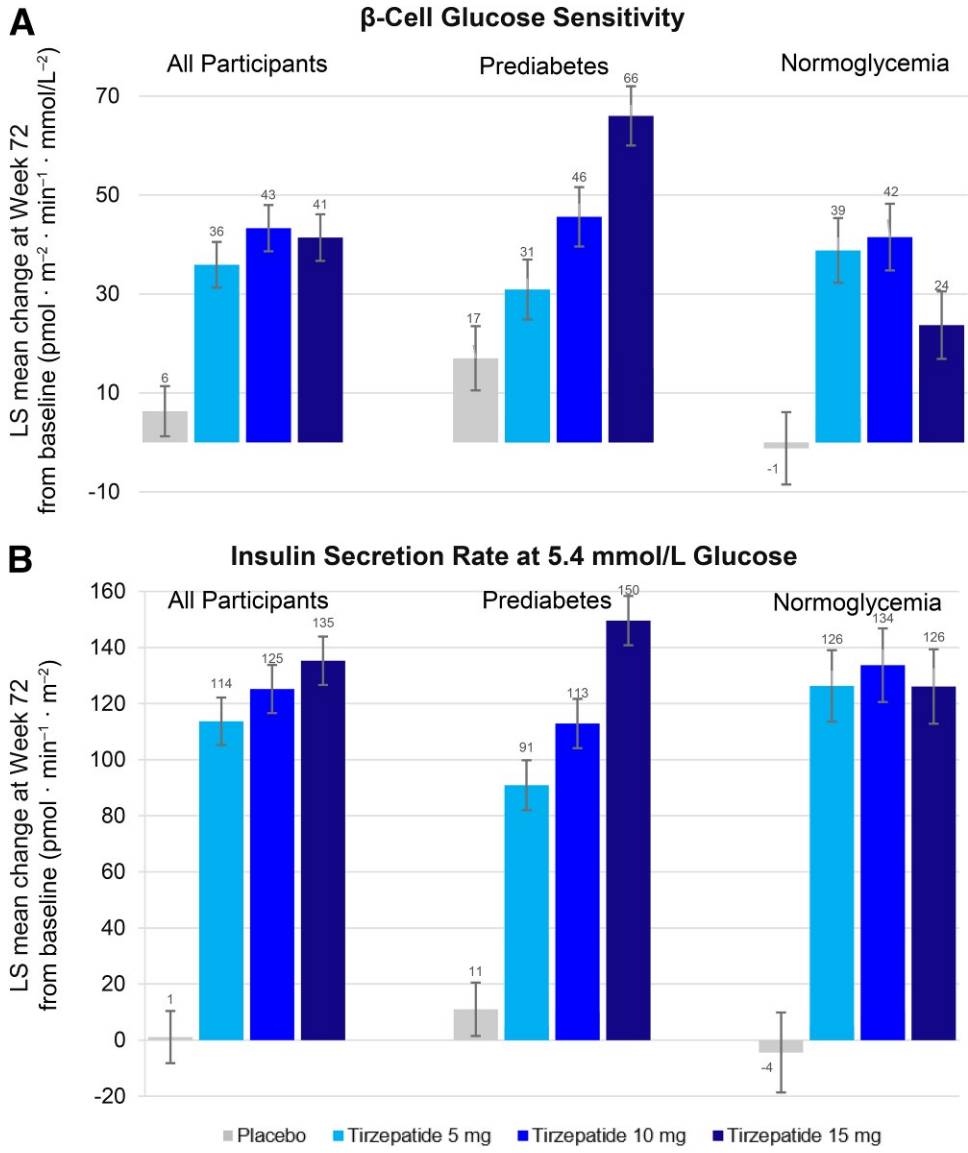

Figure 2—Changes in modeled β-GS (*A*) and ISR at 5.4 mmol/L glucose (*B*) at week 72 from baseline for the overall SURMOUNT-1 study population and by glycemic status at baseline. Data are least-squares (LS) mean ± SE. For both outcomes, changes were significantly greater for all tirzepatide groups compared with placebo, irrespective of glycemic status ($P < 0.05$), except for β-GS in participants with prediabetes treated with tirzepatide 5 mg (P = ns).

was estimated from the OGTT by the Matsuda index (8) and oral glucose insulin sensitivity (OGIS) (9). The HOMA for insulin resistance (IR), version 2 (HOMA2-IR) index was computed from fasting glucose and insulin at all time points.

Statistical Analysis

All measures were analyzed with data from randomized participants (intention-to-treat population). Data are presented as mean ± SD unless otherwise noted. Analysis for baseline measures was performed using a two-sample *t* test for continuous variables and the χ^2 test for categorical variables. An ANCOVA model and mixed models for repeated measures were conducted with baseline outcome measure, age, sex, country, visit, prediabetes status, and tirzepatide dose as fixed effects for change from baseline to the end point and change from baseline with repeated values, respectively. Details regarding study methodology are provided in the Supplementary Material.

RESULTS

Baseline Demographics and Clinical Characteristics

Baseline characteristics of participants are presented in Supplementary Tables 1 and 2. Baseline HbA_{1c}, glucose, insulin, and HOMA2-IR were higher among participants with prediabetes than those with normoglycemia at baseline, while indices of β-cell function (β-GS, β-RS, and IGI) and insulin sensitivity were lower (all $P < 0.001$).

Changes Over Time in HbA_{1c}, Glucose, Insulin, Body Weight, and HOMA2-IR

Significant reductions in HbA_{1c}, glucose, insulin, and body weight were observed with all tirzepatide doses compared with placebo (Supplementary Fig. 1*A*–*D*), consistent with previous findings (1). For all parameters, separation of curves between

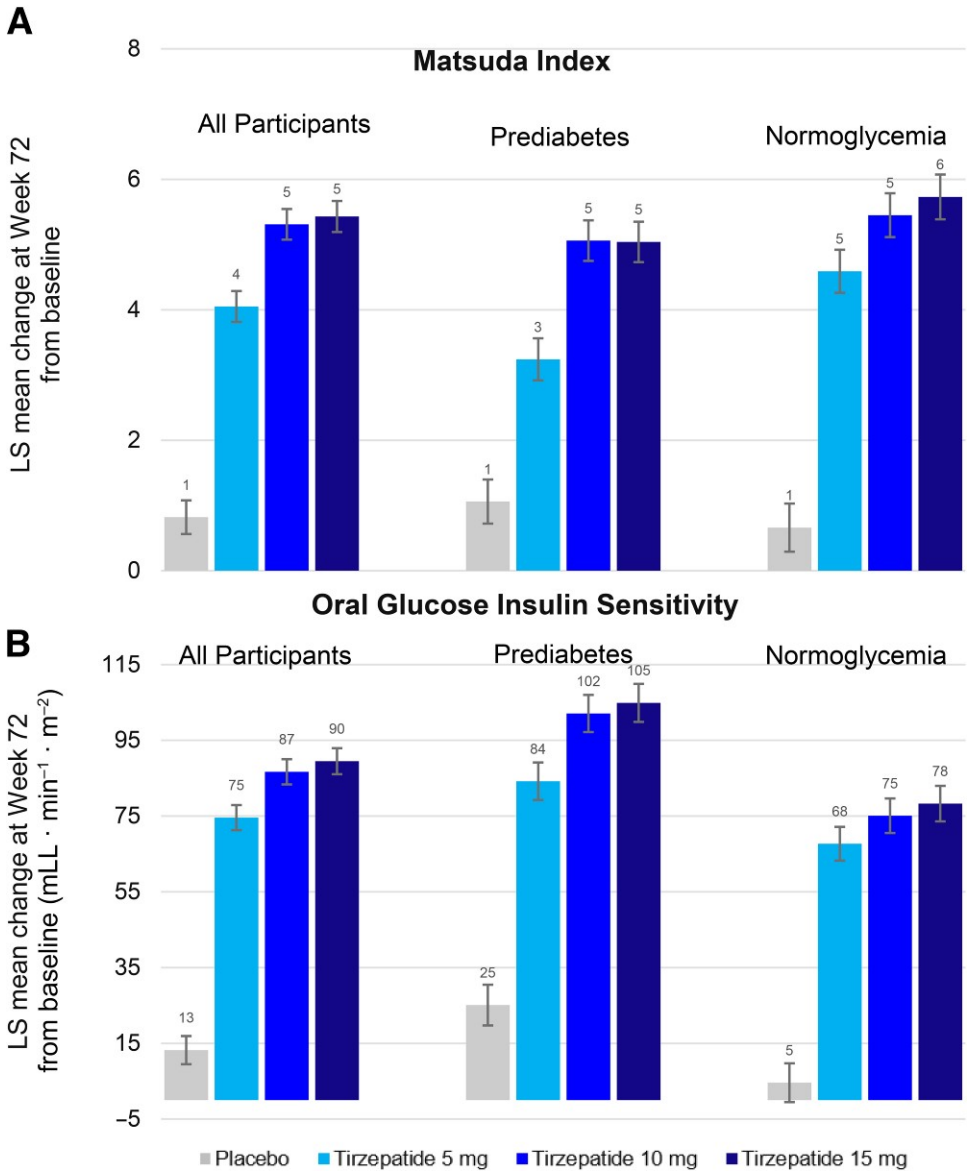

Figure 3—Changes in the Matsuda index (*A*) and OGIS (*B*) at week 72 from baseline for the overall SURMOUNT-1 study population and by glycemic status at baseline. Data are least-squares (LS) mean ± SE. For both outcomes, changes were significantly greater with tirzepatide compared with placebo, irrespective of glycemic status ($P < 0.001$).

tirzepatide and placebo occurred within the first 12 weeks of treatment. Dose dependence of these changes was small. Response to treatment occurred irrespective of baseline glycemic status.

HOMA2-IR decreased over time in all tirzepatide groups, irrespective of glycemic status, reaching near-plateau levels after ∼36 weeks of treatment. At week 72, HOMA2-IR in participants with prediabetes was approaching that of participants with normoglycemia (Supplementary Fig. 1*E*).

Changes in Glucose Tolerance

Tirzepatide treatment of 72 weeks was associated with significantly reduced glucose and insulin AUC during the OGTT, irrespective of baseline glycemic status (Fig. 1*A* and *B*, respectively). Glucose AUC reductions were greater among participants with prediabetes than those with normoglycemia.

Changes in β-Cell Function

Tirzepatide treatment was associated with significantly increased β-GS across doses and subgroups (all $P < 0.001$) (Fig. 2*A*). Dose-related $ISR_{5.4\,mmol/L}$ increases in response to tirzepatide, compared with placebo, were observed in the overall population and in participants with prediabetes but not in participants with normoglycemia (Fig. 2*B*). At week 72, there was a statistically significant decrease in TIS in participants treated with tirzepatide compared with placebo, irrespective of baseline glycemic status (data not shown). Significantly greater increases in the potentiation ratio at the 2-h time point during the OGTT were observed across most, but not all, tirzepatide groups versus placebo, largely irrespective of glycemic status (data not shown). Significantly greater increases in the 30-min IGI were observed in the overall population and in participants with normoglycemia assigned to tirzepatide 10 and 15 mg, but not 5 mg, compared with placebo. Among participants with prediabetes, there was no difference between

Table 1—Multivariate analysis of β-cell function, insulin sensitivity, and glycemic parameters in participants of the SURMOUNT-1 clinical trial

	Δβ-GS		$\Delta ISR_{5.4\ mmol/L}$		ΔMatsuda index		ΔOGIS		ΔHbA_{1c}		ΔGlucose	
	PRC	*P* value	PRC	*P* value	PRC	*P* value	PRC	*P* value	PRC	*P* value	PRC	*P* value
Age	−0.28	0.19	−0.34	0.37	−0.01	0.39	−0.15	0.27	+0.001	0.0003	+0.02	0.048
Prediabetes (yes vs. no)	−1.29	0.90	+3.00	0.87	−0.01	0.98	−21.37	0.0023	+0.09	<0.0001	+5.56	<0.0001
Tirzepatide pooled	+32.41	0.0009	+65.6	0.0002	+0.15	0.74	+16.52	0.010	−0.11	<0.0001	−2.46	<0.0001
ΔPercentage weight	+0.30	0.69	−0.86	0.53	−0.24	<0.0001	−4.17	<0.0001	+0.01	<0.0001	+0.20	<0.0001
ΔPercentage weight × tirzepatide	−0.44	0.59	−2.68	0.07	−0.005	0.88	+1.08	0.039	−0.001	0.43	0.005	0.91

Data are presented as partial regression coefficients (PRC) and corresponding *P* values adjusted for sex, country, and visit. Tirzepatide is tirzepatide treatment (pooled doses); Δ indicates changes at week 72 from baseline. ΔGlucose is the percentage change of fasting glucose concentrations at week 72; ΔPercent weight × tirzepatide is the interaction term between treatment with tirzepatide (yes/no) and body weight change.

any tirzepatide dose compared with placebo (Supplementary Fig. 2).

For β-RS, there was no difference in change after 72 weeks in any tirzepatide group versus placebo for overall, prediabetes, and normoglycemia populations (data not shown).

Changes in Insulin Sensitivity

Improvements in insulin sensitivity after 72 weeks, as assessed using the Matsuda index or OGIS, were observed with all tirzepatide doses for the overall, prediabetes, and normoglycemia populations (Fig. 3).

Impact of Age, Glycemic Status, Tirzepatide Treatment, and Change in Body Weight on Insulin Sensitivity, β-Cell Function, and Glycemic Parameters

In multivariate analyses (Table 1), changes in the Matsuda index and OGIS were inversely related to the percentage change in body weight ($P < 0.001$). OGIS changes were smaller in participants with prediabetes than in those with normoglycemia when adjusted for weight change. In multivariate analyses, no statistically significant association was observed with prediabetes and change in the Matsuda index. A significant interaction between treatment and percentage change in body weight was observed for OGIS ($P = 0.039$), indicating a treatment effect independent of weight loss; however, no such association was found for the Matsuda index.

Changes in β-cell function measures (β-GS and $ISR_{5.4\ mmol/L}$) were associated with tirzepatide treatment but not with body weight changes.

Regarding decreases in HbA_{1c} and the percentage change in fasting glucose, greater weight reduction and tirzepatide treatment were associated with greater reductions in these parameters, while older age and prediabetes were associated with smaller reductions.

CONCLUSIONS

This post hoc analysis of the SURMOUNT-1 trial is the first study in individuals with overweight or obesity but without diabetes to investigate the association between tirzepatide and insulin sensitivity and β-cell function in relation to weight loss. Results show that 72-week treatment with tirzepatide was associated with improved OGTT-assessed insulin sensitivity and β-cell function across all investigated doses of tirzepatide (5, 10, and 15 mg) in participants with either baseline prediabetes or normoglycemia. Notably, participants with baseline normoglycemia, who had higher insulin sensitivity at baseline, experienced a twofold increase in the Matsuda index.

The β-cell function improvement is consistent with previous findings in individuals with type 2 diabetes (4,10) and with the mechanisms of action for tirzepatide (11). Of note, a clear increase in β-cell function (as $ISR_{5.4\ mmol/L}$) was observed in participants with normoglycemia who had normal baseline β-cell function. The β-cell function improvement was not associated with weight loss in multiple regression analysis.

Conversely, the insulin sensitivity increase was strongly associated with weight reduction, as expected. However, multiple regression analysis using OGIS suggests a possible effect of tirzepatide independent from weight reduction. This effect could be, in part, a result of GIP receptor activation. In people with type 2 diabetes, treatment with the selective long-acting GIP RA macupatide produced a larger insulin sensitivity improvement compared with the selective GLP-1 RA dulaglutide, despite similar weight reduction, and combination therapy with these agents had additive effects on insulin sensitivity (12). Greater insulin sensitivity improvement per unit of weight reduction was also observed with tirzepatide versus the selective GLP-1 RA semaglutide (13).

Considering the observed effects of tirzepatide in the context of mechanisms leading to type 2 diabetes, it could be inferred that tirzepatide treatment may protect against progression toward dysglycemia, due to the concomitant improvement in insulin sensitivity and β-cell function, leading to normalization of glucose levels in people with prediabetes, thereby possibly preventing β-cell deterioration. The 3-year SURMOUNT-1 study in individuals with obesity and prediabetes showed that tirzepatide treatment markedly reduced the risk of progression to type 2 diabetes compared with placebo, supporting this hypothesis (14).

Study limitations should be acknowledged. These are post hoc analyses. OGTT data were available only at baseline and after 72 weeks, thus preventing the assessment of changes over time in β-cell function and insulin sensitivity beyond HOMA2-IR. As only a small percentage of participants met the definition of overweight, the results may not be representative of this weight category. Although race and ethnicity among U.S. participants was representative of U.S. demographics,

70% of participants were White. In addition, the study did not include a selective GLP-1 RA for comparison, limiting the possibility to investigate the role of GIP receptor activation.

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Author Contributions. A.M., X.M., E.S.L., L.F., M.C.B., and E.F. were responsible for data analysis. A.S. provided medical oversight during the trial. A.S., X.M., E.S.L., L.F., C.J.L., M.K.T., and M.C.B. had full access to the data. A.S., M.K.T., and M.C.B. contributed to the study design. A.S. and M.C.B. were responsible for data acquisition. All authors, including D.H.v.R., participated in interpretation of the data, critical review of the manuscript, and approved this manuscript to be submitted for publication. A.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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