Reductions in Insulin Resistance are Mediated Primarily via Weight Loss in Subjects With Type 2 Diabetes on Semaglutide

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Context: Semaglutide, a once-weekly glucagon-like peptide-1 analog approved for use in patients with type 2 diabetes (T2D), demonstrated superior body weight (BW) reductions and decreased insulin resistance (IR) vs comparators across the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) 1–3 clinical trials.

Objective: To investigate the relationship between IR and BW across the SUSTAIN 1–3 trials.

Design: *Post hoc* analysis of the SUSTAIN 1–3 trials.

Setting: Three hundred and eleven sites in 30 countries.

Patients or other participants: 2432 subjects with T2D.

Interventions: Semaglutide 0.5 or 1.0 mg, placebo or active comparator (sitagliptin 100 mg, exenatide extended release 2.0 mg).

Main Outcome Measure: To assess the extent of the effect on IR that is mediated (indirect effect) and not mediated (direct effect) by the effect on BW.

Results: Across SUSTAIN 1–3, mean BW was significantly reduced with semaglutide 0.5 mg (3.7 kg to 4.3 kg; $P < 0.0001$) and semaglutide 1.0 mg (4.5 kg to 6.1 kg; $P < 0.0001$) vs comparators (1.0 kg to 1.9 kg). There were greater reductions in IR with semaglutide 0.5 mg (27% to 36%) and semaglutide 1.0 mg (32% to 46%) vs comparators (17% to 28%). Greater reductions in BW were generally associated with greater decreases in IR. The effect on IR was primarily mediated by weight loss (70% to 80% and 34% to 94%, for semaglutide 0.5 mg and 1.0 mg, respectively, vs comparator).

Conclusions: Semaglutide consistently reduced BW and IR in subjects with T2D in SUSTAIN 1–3. In this analysis, IR improvement was positively associated with, and primarily mediated by, the effect of semaglutide on BW. **(*J Clin Endocrinol Metab* 104: 4078–4086, 2019)**

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Abbreviations: BMI, body mass index; BP, blood pressure; BW, body weight; CVD, cardiovascular disease; Exenatide ER, exenatide extended release; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; IR, insulin resistance; OAD, oral antidiabetic drug; SUSTAIN, Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes trial; T2D, type 2 diabetes; WL, weight loss.

The link between insulin resistance (IR) and type 2 diabetes (T2D) is widely recognized (1). Evidence suggests that IR is one of the common underlying pathophysiological abnormalities of T2D and also contributes to the development of cardiovascular disease (CVD) (2). Weight loss (WL) has been shown to improve IR, and maintenance of body weight (BW) reductions results in sustained insulin sensitivity (3).

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are effective at reducing glycated hemoglobin (HbA_{1c}), BW, and blood pressure (BP), with a low risk of hypoglycemia (4). Studies have indicated that, in addition, GLP-1RAs decrease IR (5, 6). However, the exact mechanisms behind the reduction in IR remain to be fully elucidated.

Semaglutide (Novo Nordisk, Denmark), a once-weekly, subcutaneous glucagon-like peptide-1 (GLP-1) analog approved for the treatment of T2D (7), was evaluated in the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) phase 3 clinical trial program (8–14). In the SUSTAIN trials, subjects treated with semaglutide achieved clinically relevant and significant reductions in HbA_{1c} and BW from baseline.

The aim of this *post hoc* analysis was to examine the relationship between IR and BW across the SUSTAIN 1–3 trials, in which IR was assessed as an outcome (8–10). Mediation analyses were conducted, in addition to standard regression analyses, to gain a greater understanding of potential causality.

Materials and Methods

IR data were available for SUSTAIN 1–3, but unavailable for SUSTAIN 4–7 (11–14), therefore, these latter trials were not included in the present analysis.

Trial designs

The trial designs of SUSTAIN 1–3 have been previously reported in full (8–10). Briefly, adults with T2D were randomized to receive semaglutide or comparators for 30 weeks (SUSTAIN 1) or 56 weeks (SUSTAIN 2 and 3). Comparators were placebo, sitagliptin 100 mg, and exenatide extended release (ER) 2.0 mg, respectively (8–10).

Semaglutide subcutaneous 0.5 mg and 1.0 mg were administered in all trials except for SUSTAIN 3, in which only the 1.0 mg dose was given. All semaglutide-treated subjects followed a fixed dose-escalation regimen. The semaglutide 0.5 mg maintenance dose was reached after four weeks of semaglutide 0.25 mg once weekly, and the semaglutide 1.0 mg maintenance dose was reached after an additional four weeks of 0.5 mg once weekly (8–10).

In SUSTAIN 1, subjects were treatment-naïve and received no antidiabetic background treatment. In SUSTAIN 2 and 3, subjects were on a background of oral antidiabetic drugs (OADs), which included either metformin and/or thiazolidinediones (SUSTAIN 2), or one or two of metformin, thiazolidinediones, or sulfonylureas (SUSTAIN 3).

All trials were conducted in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki (15, 16). The protocols were approved by local ethics committees and institutional review boards.

Subject population

Subjects in the SUSTAIN 1–3 trials were ≥18 years of age and diagnosed with T2D (baseline HbA_{1c} inclusion criteria were 7.0% to 10.0% for SUSTAIN 1 and 7.0% to 10.5% for SUSTAIN 2 and SUSTAIN 3).

Key exclusion criteria were history of chronic or idiopathic acute pancreatitis; known proliferative retinopathy or maculopathy requiring acute treatment; screening calcitonin value ≥50 ng/L; personal and/or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; acute coronary or cerebrovascular event within 90 days before randomization; and heart failure (New York Heart Association class IV). Written informed consent was obtained from all subjects before trial commencement.

Study end points

The primary end point in SUSTAIN 1–3 was change in HbA_{1c} from baseline to end of treatment (30 or 56 weeks) (8–10). The secondary end points presented in this *post hoc* analysis were change from baseline to end of treatment (30 or 56 weeks) in BW and IR, with the latter assessed using homeostatic model assessment of insulin resistance (HOMA-IR; all fasting) (17). The fasting HOMA end point was calculated as follows: fasting HOMA-IR (%) = fasting insulin [μU/mL] × fasting plasma glucose (FPG) [mmol/L]/22.5. Safety end points (including adverse events and hypoglycemia) were also assessed.

Statistical analysis, including mediation analysis

Observations for all randomized and exposed subjects (full analysis set) while on treatment and not taking rescue medication were used in the statistical analyses.

Changes in BW from baseline to end of treatment were analyzed using mixed models for repeated measurements, with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

Values for IR were log-transformed before analysis. The log-transformed post-baseline responses were analyzed using mixed models for repeated measurements, as were the changes from baseline in BW data.

From these models, estimated treatment differences (BW) and ratios (HOMA-IR) were calculated (semaglutide vs comparators).

When summarizing change in IR by weight change, weight-change categories were chosen to ensure there were sufficient numbers of subjects in each group. These categories were: WL > 4 kg, WL >0 to 4 kg, and weight gain ≥0 kg. For these summaries, missing data were imputed from the mixed models for repeated measurements.

An imputation-based mediation analysis was performed to quantify the extent to which improvement in HOMA-IR from baseline to end of treatment was mediated (indirect/WL-mediated effect) or not (direct/non-WL–mediated effect) by weight change from baseline to end of treatment (18).

The natural effect model for the estimation of direct and indirect effects included the interaction between treatment and

WL, with the baseline variables BW, IR, and country as main effects, assuming no interaction between natural effects and baseline variables.

In addition to the variables included in the natural effect model, the model used to impute counterfactual values of IR also included the interaction between treatment and each baseline variable, and the interaction between WL and each baseline variable (18). Values for IR were log-transformed before analysis. Confidence intervals were percentile bootstrap estimates. Missing data were imputed from the mixed models for repeated measurements. Proportions mediated were calculated as the estimated indirect effect (as a relative reduction) divided by the estimated total effect (as a relative reduction).

Results

Subject disposition and baseline characteristics

In total, 2432 subjects with T2D were randomized to semaglutide 0.5 mg or 1.0 mg once weekly or comparators (Table 1) (8–10). Of these, 2421 (>99%) subjects were exposed to trial medication and 2265 (93%) completed the trials. The proportion of subjects who discontinued treatment prematurely ranged from 13.0% to 13.3% with semaglutide 0.5 mg, 12.3% to 20.3% with semaglutide 1.0 mg, and 7.9% to 21.0% with comparators (Table 1). Premature treatment discontinuation was higher in SUSTAIN 3 than in SUSTAIN 1 and 2 (Table 1).

In SUSTAIN 2 and 3, subjects were on a background of diabetes medications including metformin (>96%), sulfonylureas (48.1% SUSTAIN 3), and thiazolidinediones (44.9% SUSTAIN 2; 2.3% SUSTAIN 3) (Table 1) (8–10).

Overall, 236 (9.7%) subjects received rescue medication. A greater proportion of subjects on comparator treatments received rescue medication (11.9% to 20.9%) than those on semaglutide 0.5 mg and 1.0 mg (2.4% to 7.2%) (Table 1).

Mean baseline HbA_{1c} (8.1% to 8.3%), age (53.7 to 56.6 years), and body mass index (BMI; 32.5 to 33.8 kg/m^2) were similar across the three trials (Table 1) (8–10). Diabetes

Table 1. Subject Disposition and Baseline Characteristics for SUSTAIN 1–3

	SUSTAIN 1: Semaglutide vs placebo	SUSTAIN 2: Semaglutide vs Sitagliptin 100 mg	SUSTAIN 3: Semaglutide vs Exenatide ER 2.0 mg
	30 Wk	56 Wk	56 Wk
Subject disposition, N (%)			
Randomized	388	1231	813
Exposed	387 (99.7)	1225 (99.5)	809 (99.5)
Trial completers	359 (92.5)	1163 (94.5)	743 (91.4)
Premature treatment discontinuation			
Semaglutide 0.5 mg	17 (13.3)	53 (13.0)	N/A
Semaglutide 1.0 mg	16 (12.3)	61 (14.9)	82 (20.3)
Comparator	14 (10.9)	32 (7.9)	85 (21.0)
Subjects administered rescue medication			
Semaglutide 0.5 mg	6 (4.7)	25 (6.1)	N/A
Semaglutide 1.0 mg	6 (4.6)	10 (2.4)	29 (7.2)
Comparator	27 (20.9)	85 (20.9)	48 (11.9)
Diabetes medications at randomization, n (%)	N/A		
Metformin/biguanides		1216 (99.3)	781 (96.5)
Sulfonylureas		2 (<1)	389 (48.1)
TZDs		66 (5.4)	19 (2.3)
Metformin plus TZDs		60 (4.9)	16 (2.0)
Other BG-lowering drugs		N/A	3 (<1)
Combinations of oral blood glucose-lowering drugs		1 (<1)	N/A
Long-acting insulins and analogs for injection		N/A	1 (<1)
Baseline characteristics, mean (SD)			
Age, y	53.7 (11.3)	55.1 (10.0)	56.6 (10.7)
Male, %	54.3	50.6	55.3
Diabetes duration, y	4.2 (5.5)	6.6 (5.1)	9.2 (6.3)
Body weight, kg	91.9 (23.8)	89.5 (20.3)	95.8 (21.5)
HbA_{1c}, %	8.1 (0.9)	8.1 (0.9)	8.3 (1.0)
FPG, mmol/L	9.7 (2.7)	9.4 (2.3)	10.5 (2.7)
PPG increment, mmol/L	2.5 (2.2)	2.8 (2.1)	2.2 (1.9)
BMI, kg/m^2	32.9 (7.7)	32.5 (6.2)	33.8 (6.7)

The full analysis set included all randomized subjects who received ≥1 dose of semaglutide or comparator. Trial completers included all subjects with a follow-up visit.

Abbreviations: BG, blood glucose; N/A, not applicable; PPG, postprandial glucose; TZD, thiazolidinedione.

duration at baseline differed between the trials: duration was shortest (4.2 years) in SUSTAIN 1 (treatment-naïve subjects) and longest (9.2 years) in SUSTAIN 3 (Table 1).

Body weight

Mean BW across the SUSTAIN 1–3 trials (baseline 89.5 to 95.8 kg) decreased significantly from baseline to end of treatment, by 3.7 to 4.3 kg with semaglutide 0.5 mg and by 4.5 to 6.1 kg with semaglutide 1.0 mg, compared with 1.0 kg, 1.9 kg, and 1.9 kg with placebo, sitagliptin, and exenatide ER in SUSTAIN 1, 2, and 3, respectively ($P < 0.0001$ vs all comparators; Fig. 1).

Insulin resistance

Overall, IR decreased by 27.3% to 36.0% with semaglutide 0.5 mg and by 32.4% to 45.9% with semaglutide 1.0 mg, compared with 17.4%, 28.0%, and 27.9% with placebo, sitagliptin, and exenatide ER in SUSTAIN 1, 2, and 3, respectively (Fig. 2; $P < 0.05$ vs comparator for all groups except semaglutide 0.5 mg group in SUSTAIN 1).

Relationship between BW and IR, including mediation analysis

In general, when IR was summarized by weight-change category, greater reductions in IR were observed with increasing WL (Fig. 2). However, for subjects within the weight-gain category in SUSTAIN 1, an increase in IR of 5.3% was observed for semaglutide 1.0 mg. In subjects with similar WL, additional reductions in IR were generally observed with semaglutide vs comparators (Fig. 2).

A regression analysis of change in IR by weight change showed that greater reductions in BW were generally associated with greater reductions in IR (Fig. 3).

The mediation analysis (Fig. 4) showed that the proportions of the effect of semaglutide vs comparator on HOMA-IR mediated by WL were as follows: 70% for semaglutide 0.5 mg and 34% for semaglutide 1.0 mg in SUSTAIN 1; 80% for semaglutide 0.5 mg and 94% for semaglutide 1.0 mg in SUSTAIN 2; and 69% for semaglutide 1.0 mg in SUSTAIN 3.

Safety

Semaglutide was well tolerated and demonstrated a safety profile similar to other GLP-1RAs (19, 20). The most frequent adverse events with semaglutide were gastrointestinal; these were mainly mild or moderate and generally decreased in frequency over time. Nausea was the most common adverse event observed with semaglutide. In SUSTAIN 1–3, severe or blood glucose-confirmed symptomatic hypoglycemia events were fewer or similar with semaglutide vs comparators, irrespective of background OAD treatment. No unexpected safety issues were identified (8–10).

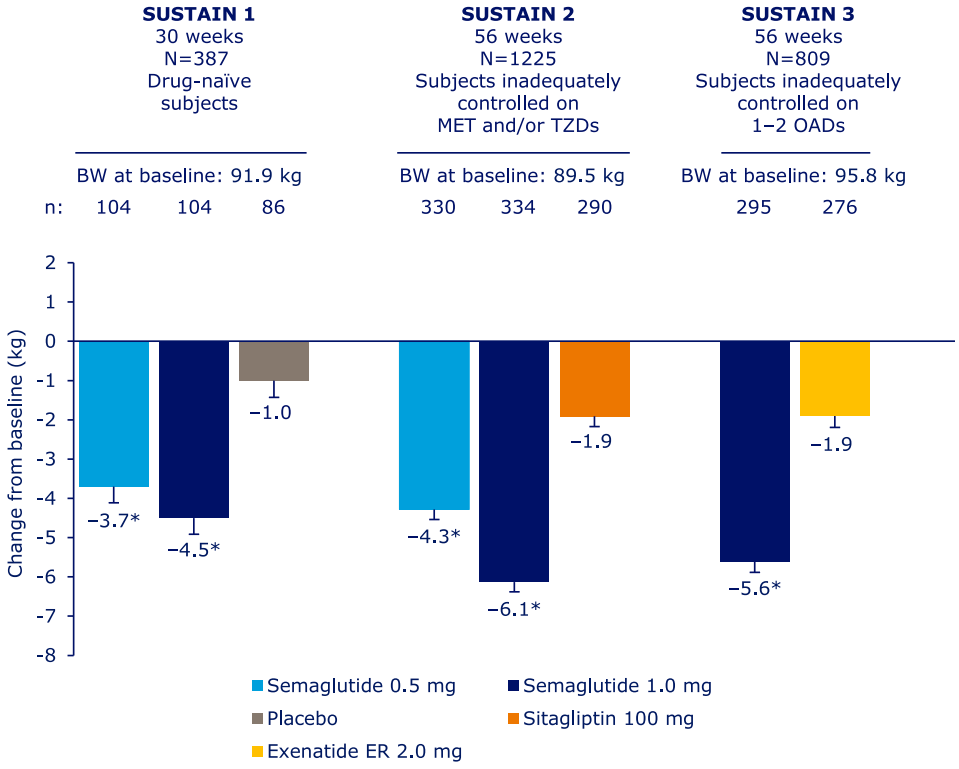

Figure 1. Mean change in BW (kg) from baseline to end of treatment ± SE in the SUSTAIN 1–3 trials. *$P < 0.0001$ vs comparator. Based on "on-treatment without rescue medication" data from subjects in the full analysis set. Mean change in BW was estimated using a mixed model for repeated measurements that included treatment, country, and baseline BW as variables, all nested within visit. n: number of subjects with valid observation at landmark visit; N: full analysis set. MET, metformin; TZD, thiazolidinedione.

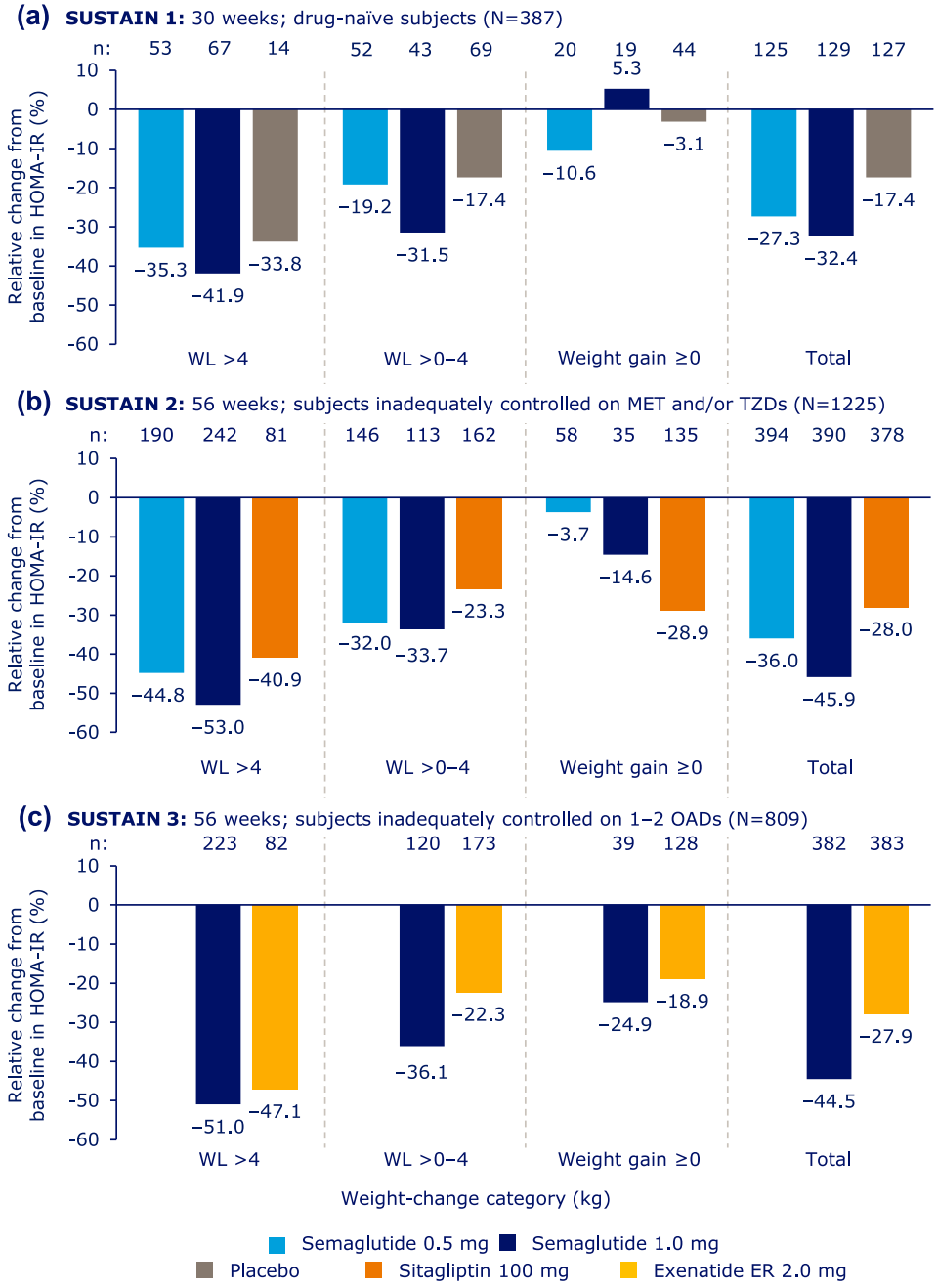

Figure 2. Change in IR from baseline to end of treatment in (a) SUSTAIN 1, (b) SUSTAIN 2, and (c) SUSTAIN 3 by weight-change category. Based on "on-treatment without rescue medication" data from subjects in the full analysis set, with missing data imputed from a mixed model for repeated measurements. Weight-change categories were chosen to ensure sufficient subject numbers in each group. Relative change from baseline in HOMA-IR (%) was calculated from the geometric mean ratio to baseline. Values were analyzed on a logarithmic scale and back-transformed into the original scale. Dashed lines represent change in WL category. n: subjects contributing to summary; N: full analysis set. MET, metformin; TZD, thiazolidinedione.

Discussion

These analyses of the SUSTAIN 1–3 trials, in which HOMA-IR data were available, showed that semaglutide treatment consistently reduced both BW and IR in subjects with T2D. In addition, *post hoc* analyses showed that, overall, semaglutide reduced IR across weight-change categories, with greater WL generally being associated with greater reductions in IR. The reductions in IR observed with semaglutide vs comparators were primarily mediated by the effect on BW.

Our findings correspond with those of other studies, which have shown that decreased IR is related to WL (21–23). Indeed, WL has been shown to be the strongest predictor of improved insulin sensitivity, whereas weight regain predicted reduced insulin sensitivity (increased IR) (3). However, few studies have evaluated whether the improvement in IR is mediated by an inherent action of the study drug

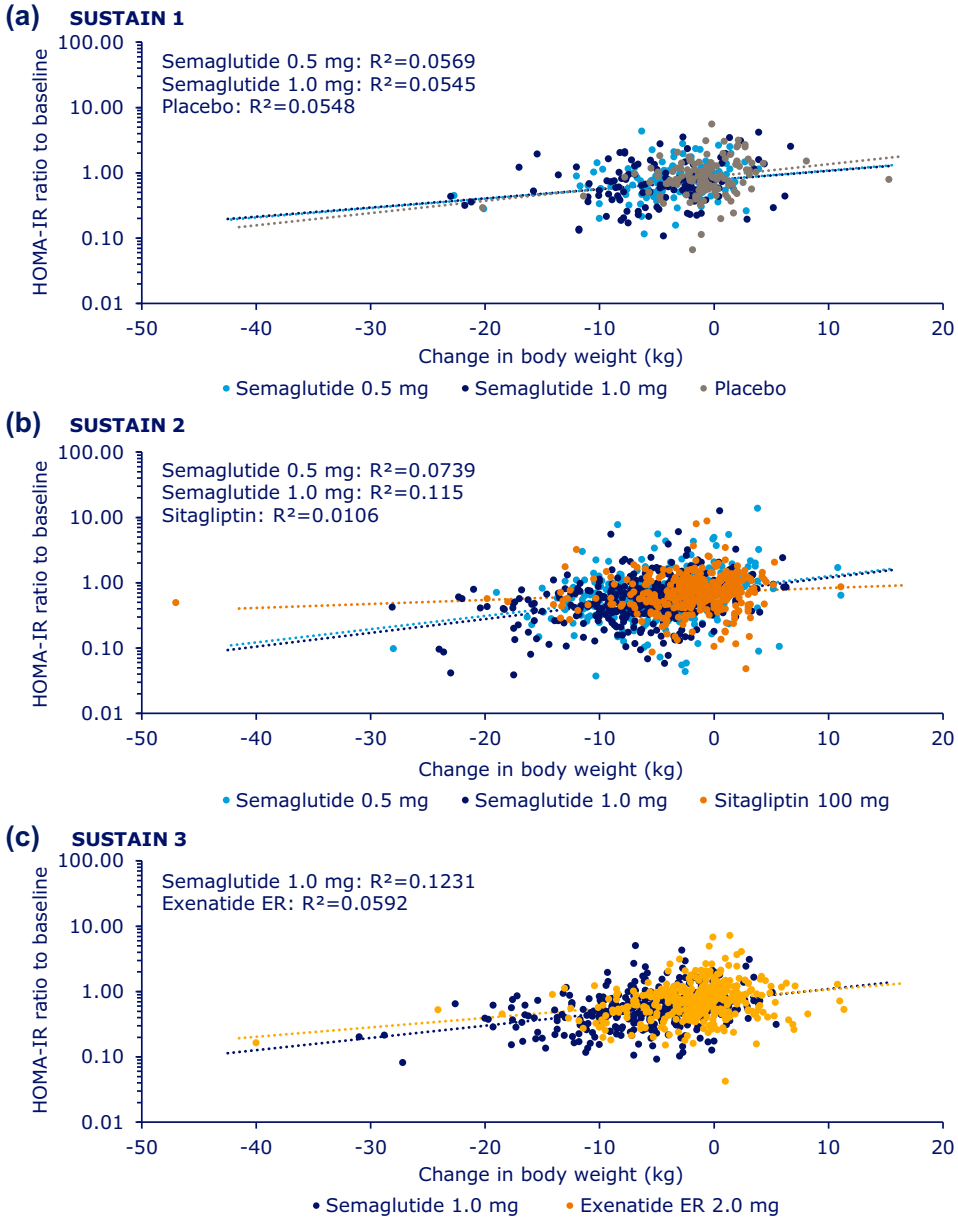

Figure 3. Relationship between BW and IR in (a) SUSTAIN 1, (b) SUSTAIN 2, and (c) SUSTAIN 3. "On-treatment without rescue medication" data are shown, with missing data imputed from a mixed model for repeated measurements. Dotted lines show regression lines fitted for each treatment separately on log-transformed IR values. Regression equations for SUSTAIN 1: semaglutide 0.5 mg $y = 0.8498e^{0.0352x}$, semaglutide 1.0 mg $y = 0.7790e^{0.0324x}$, placebo $y = 0.8846e^{0.0431x}$; for SUSTAIN 2: semaglutide 0.5 mg $y = 0.7912e^{0.0467x}$, semaglutide 1.0 mg $y = 0.7385e^{0.0486x}$, sitagliptin $y = 0.7251e^{0.0141x}$; for SUSTAIN 3: semaglutide 1.0 mg $y = 0.7114e^{0.043x}$, exenatide ER $y = 0.7704e^{0.0334x}$. The y-axes scales are logarithmic.

itself—which would support the claim for an insulin-sensitizing effect of the drug—or indirectly by drug-induced WL.

Regression analysis shows the extent to which a dependent variable (relative change in HOMA-IR) is predicted by the independent variable (change in BW). The results from the SUSTAIN 1–3 trials (Fig. 3) show that greater reductions in BW were generally associated with greater reductions in IR. However, the goodness-of-fit of the data to the regression line (R^2) does not provide any information on the potential causal relationship between the variables.

A mediation analysis was also undertaken to quantify the relative contributions of direct and indirect effects of semaglutide on observed changes in IR. Although the mediation analysis showed a relationship between semaglutide-mediated WL and IR, it is important to emphasize that the results of mediation analyses, by nature, do not necessarily imply causation (24). Unlike the individual effects of semaglutide on WL and IR, the effect on HOMA-IR mediated by semaglutide-induced WL in the mediation analysis was not dose dependent. This is because the mediation analysis quantified the

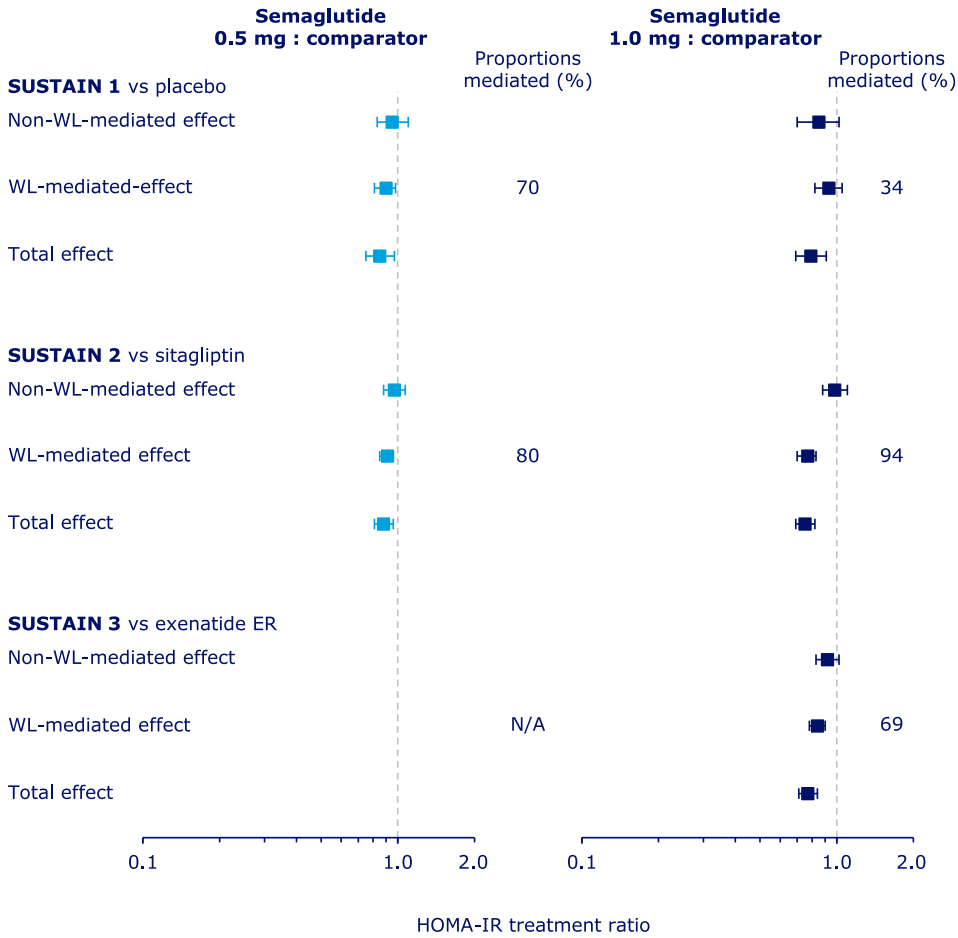

Figure 4. Improvement in insulin resistance at end of treatment mediated, or not mediated, by weight change. Based on "on-treatment without rescue medication" data from subjects in the full analysis set, with missing data imputed from a mixed model for repeated measurements. The effects were estimated using an imputation-based mediation analysis (18). Mean estimates and 95% CIs are calculated on log-scale and back-transformed to original scale. N/A, not applicable.

proportion of the treatment effect (semaglutide vs placebo) on the relative change in HOMA-IR that was mediated by an effect on change in BW, and this would not be expected to be dose dependent. Additionally, variability in the estimates would be expected because of the low numbers. The current analysis also quantified an effect of semaglutide on IR that was not mediated by WL, which implies that other factors are involved. One such factor may be FPG. As already noted, FPG, together with fasting insulin, contributes to the calculated value of HOMA-IR; it therefore follows that any intervention that lowers fasting glucose will also tend to reduce HOMA-IR values. This may explain why we saw reductions in HOMA-IR even in the absence of WL (Fig. 2) and underlines the need for considered interpretation of HOMA-IR as a surrogate marker of insulin sensitivity (17, 25, 26).

Another factor that may contribute to the reduction in IR is the suppression of glucagon secretion. After 12 weeks of treatment, semaglutide has been shown to reduce both fasting and postprandial glucagon compared with placebo in a 24-hour meal test in subjects with T2D (27). The concept of semaglutide mediating effects on IR via BW and also FPG and glucagon is in keeping with the belief that GLP-1RA treatment improves β-cell function via multiple mechanisms of action (28).

The finding of significant decreases in IR with semaglutide may have important implications for current practice, given that IR is associated with both the pathophysiology of T2D and several of the complications associated with the disease, such as hypertension, dyslipidemia, and CVD (29). Indeed, IR has been shown to be an independent predictor of CVD in T2D (30). It could be that the effect on IR, together with several other known mechanisms, contributes to the beneficial effects of semaglutide on glucose metabolism and CVD.

A limitation of this analysis was that HOMA-IR—which is an indirect measure (17)—was used to estimate IR, rather than the gold standard hyperinsulinemic euglycemic glucose clamp (31). Because the liver is the primary regulator of glucose in the basal state, HOMA-IR tends to reflect hepatic insulin action more closely than whole-body (including

skeletal) insulin sensitivity (26). Furthermore, as HOMA-IR is based on both basal insulin and plasma glucose concentrations, caution may be warranted in the interpretation of HOMA-IR findings in insulin-deficient patients. Plasma insulin decreases over time in patients with diabetes, unlike IR, and therefore HOMA-IR tends to underestimate IR in patients with long-term diabetes. There is a constant denominator in the HOMA-IR formula adjusting for diabetes, based upon assumptions on the values of fasting plasma insulin and glucose in a "normal" patient (17) but this does not address these issues fully. Nevertheless, extensive research has found HOMA-IR to be a reliable surrogate marker of IR that correlates well with results obtained from euglycemic-hyperinsulinemic clamp studies (32, 33). As such, HOMA-IR is used widely in randomized controlled trials in T2D (26, 34, 35). Another limitation is the different time points (30 weeks for SUSTAIN 1 and 56 weeks for SUSTAIN 2 and 3), obtained from the prespecified trial end points, that were included in the analysis. A strength of this analysis is the high proportion of subjects who lost weight in the SUSTAIN trials vs those who experienced weight gain, which allowed for robust statistical modeling of the relationship between WL and IR.

Further studies are warranted to elucidate fully the mechanism by which GLP-1RAs reduce IR, and to determine the extent to which such reductions underpin the clinical benefits of this drug class. Nevertheless, the findings of this current analysis indicate the potential of semaglutide, which is associated with significant WL as well as improvements in IR, to slow the progression of T2D and, through IR reduction, positively impact the comorbidities associated with the disease.

Conclusions

Treatment with semaglutide consistently reduced BW and IR in subjects with T2D in the SUSTAIN 1–3 trials. IR improvement was positively associated with WL. The reductions in IR with semaglutide vs comparators were primarily mediated by the effect of semaglutide on BW.

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