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Effect of Semaglutide on Insulin Dose Reduction in Adults With Type 1 Diabetes and Obesity Using Automated Insulin Delivery Systems: ADJUST-T1D Post Hoc Analysis

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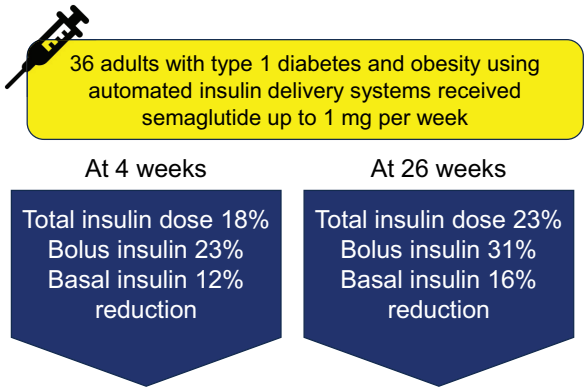

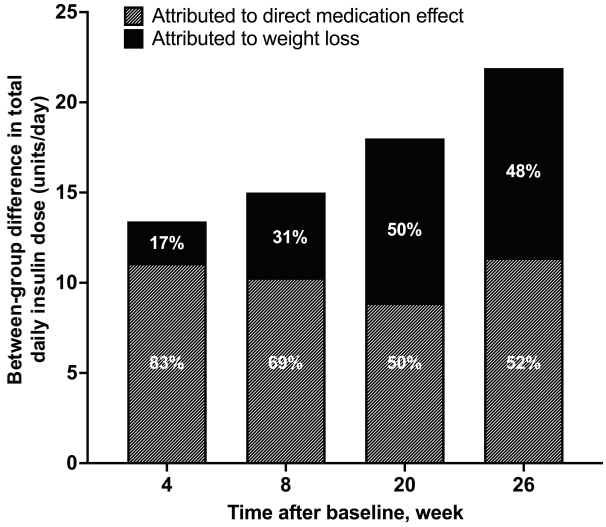

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  The relationship among insulin dosing, glycemic improvement, and weight loss during semaglutide therapy in adults with type 1 diabetes and obesity is unknown.
- **What is the specific question we wanted to answer?**
  What is the association between reductions in total daily insulin dose and weight loss in individuals with type 1 diabetes and obesity?
- **What did we find?**
  Semaglutide produced rapid, sustained, and primarily bolus-driven insulin reductions. The reduction was largely weight independent in early weeks and became weight loss dependent later.
- **What are the implications of our findings?**
  Significant reductions in the insulin dose reductions (by 20–30% of total daily dose) are needed at semaglutide initiation in adults with type 1 diabetes and obesity to minimize the risk of hypoglycemia.

Effect of Semaglutide on Insulin Dose Reduction in Adults With Type 1 Diabetes and Obesity Using Automated Insulin Delivery Systems: ADJUST-T1D Post Hoc Analysis

Kagan E. Karakus,[1] Halis K. Akturk,[1] Davida Kruger,[2] Andrew Ahmann,[3] Anuj Bharvaga,[4] Christine R. Langel,[4] Courtney A. Ackeifi,[5] Jonathan Rosen,[5] Laura Pyle,[6] Janet K. Snell-Bergeon,[1] and Viral N. Shah[7,8]

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OBJECTIVE

In this post hoc analysis, we used the data from the Adjunct Semaglutide Treatment in Type 1 Diabetes (ADJUST-T1D) trial, a double-blind, multicenter, randomized, placebo-controlled trial of semaglutide 1 mg/week in adults with type 1 diabetes [[T1D]and obesity), to evaluate the relationship between insulin dose reduction and weight loss.

RESEARCH DESIGN AND METHODS

Changes between semaglutide and placebo groups over 26 weeks in total daily insulin dose (TDD), basal and bolus insulin doses, carbohydrate intake, and user-initiated bolus counts were analyzed using linear mixed models. Mediation analysis was used to attribute direct effects of semaglutide versus weight loss on insulin dose reduction.

RESULTS

From baseline to week 26, there was a significant 22.6% reduction in TDD (95% CI −28.3 to −17.0), which was driven by greater reductions in bolus insulin (−30.5%; 95% CI −39.5 to −21.5) than basal insulin (−15.6%; 95% CI −21.5 to −9.7). The basal/TDD ratio increased from 0.56 to 0.62 ($P < 0.001$) and insulin dose (in units/kg/day) decreased from 0.72 to 0.60 ($P < 0.001$) in the semaglutide group. At week 4, an 83% (−11.1 U/day) reduction in TDD was due to a direct drug effect, and 17% (−2.3 U/day) was attributed to weight loss, whereas at week 26, the difference was split evenly between direct effect (−11.4 U/day; 52%) and weight loss (−10.5 U/day; 48%). Daily carbohydrate intake decreased from 137 g (95% CI 107–167) at baseline to 107 g (95% CI 76–137) at 26 weeks.

CONCLUSIONS

Semaglutide produced rapid, sustained, and primarily bolus-driven insulin dose reductions, with early effects being largely independent of weight loss in adults with T1D and obesity.

The Adjunct Semaglutide Treatment in Type 1 Diabetes (ADJUST-T1D) trial evaluated efficacy and safety of once-weekly semaglutide in doses up to 1 mg in adults

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with type 1 diabetes (T1D) and obesity (1). Over 26 weeks, 36% of the group taking semaglutide and 0% of the control group achieved the primary composite end point, which consisted of achieving continuous glucose monitoring (CGM)–based time between 70 and 180 mg/dL (i.e., time in range [TIR]) of greater than 70% and time below 70 mg/dL of less than 4%, and weight reduction of at least 5% (1). From baseline to week 26, the adjusted group difference for the semaglutide group versus placebo for HbA_{1c} was 0.3%, for TIR was 8.8%, and for weight reduction was 8.8 kg. Notably, improvements in glycemic control and reductions in total daily insulin dose (TDD) were evident as early as 4 weeks in the semaglutide group compared with the placebo group.

Previous trials with liraglutide as an adjunct to insulin for treatment of individuals with T1D demonstrated reduced body weight, improved glycemic control, and lowered exogenous insulin requirements (2,3). However, these benefits were offset by an increased risk of symptomatic hypoglycemia. One likely reason for this was the absence of an optimized insulin titration protocol, because the trials lacked the use of CGM and automated insulin delivery (AID) systems. In contrast, the ADJUST-T1D trial used CGM and AID technology to guide a structured, detailed insulin titration protocol (1). As a result, hypoglycemia rates were comparable between semaglutide and placebo groups; basal and bolus insulin doses were carefully documented, enabling the transformation of these data to clinical practice and future research.

Thus, the ADJUST-T1D trial provided the data for addressing the interplay among insulin dosing, glycemic improvement, and weight loss during semaglutide therapy in adults with T1D and obesity. In this post hoc analysis, we examined the association between reductions in TDD and weight loss in individuals with T1D and obesity.

RESEARCH DESIGN AND METHODS

In the 26-week, double-blinded ADJUST-T1D trial, 72 adults (aged 18–65 years) with T1D who used a U.S. Food and Drug Administration–approved AID system and had a BMI of 30 kg/m^2 or higher were randomly assigned in a 1:1 ratio to receive once-weekly semaglutide (up to 1 mg) or placebo at four centers in the United States. The detailed study protocol was published previously and is available at ClinicalTrials.gov (NCT05537233) (1). Major exclusion criteria included current or planned pregnancy, use of concomitant glucose-lowering medications, and any contraindications to glucagon-like peptide-1 receptor agonist (GLP-1RA) therapy.

Participants were followed through in-person visits at weeks 4, 8, 20, and 26, during which 2-week data from insulin pumps (TDD and basal and bolus insulin doses), CGM (for CGM metrics), and weight measurements were collected. The amount of carbohydrate entries to AID systems and the number of delivered meal boluses were collected from raw data for Tandem and Medtronic systems and Glooko reports for the Omnipod 5 system. The numbers of AID-initiated automated correction boluses in Tandem Control IQ and Medtronic AID systems were also collected. The total number of boluses and the carbohydrate amounts were calculated from 30-day raw pump data and divided by the days of sampling duration to calculate number of boluses per day and carbohydrate intake per day. Semaglutide was initiated at 0.25 mg weekly for the first 4 weeks, self-administered subcutaneously by participants. The dose was increased to 0.5 mg at week 4 and further to 1 mg at week 8. Investigators were permitted to temporarily reduce the semaglutide dose in cases of intolerance. AID system settings were adjusted by investigators based on provided guidance and clinical judgment to minimize the risk of hypoglycemia during drug initiation and dose escalation.

Statistical Analysis

To assess the effect of semaglutide compared with placebo on insulin requirements over time, we calculated both the percent change and absolute unit change from baseline in TDD, basal insulin dose, and bolus insulin dose for each participant at postbaseline time points. Linear mixed-effects models were fitted for each outcome, using either percent change or absolute change as the dependent variable. Each model included fixed effects for treatment group, time, their interaction, and baseline weight as a covariate. A random intercept for participants was included to account for within-subject correlation due to repeated measurements.

Total insulin dose per kilogram of body weight (units/kg/day) was analyzed as a separate outcome using values from all time points. This model included fixed effects for treatment group, time, and their interaction, along with a random intercept for participant. Similarly, the basal to total insulin ratio, carbohydrate amount per day, and number of boluses per day were tested using mixed-effect models.

To estimate the contribution of weight loss to the reduction in TDD, a longitudinal mediation framework was applied. Two linear mixed-effects models with random intercepts for participants were specified: the first modeled weight change from baseline as the dependent variable with treatment group, time, and covariates (age, sex, baseline HbA_{1c}) as predictors; the second modeled change in TDD from baseline as the dependent variable with treatment group, time, weight change, and the same covariates as predictors. Average causal mediation effects (indirect effect via weight loss), direct effects, and total effects of treatment were estimated at each postbaseline time point. The proportion mediated was calculated as the indirect effect divided by the total effect, with 95% CIs obtained from Monte Carlo simulations. All analyses were performed in R using the lme4, emmeans, and mediation packages (4). The least square mean was reported with 95% CIs or SE. A P value <0.05 was considered statistically significant.

Data and Resource Availability

The data sets generated during and/or analyzed in this study are available from the corresponding author upon reasonable request.

RESULTS

Of 72 participants, 36 were randomized to semaglutide treatment and 36 were randomized to placebo, and 94% and 92% completed the study at 26 weeks, respectively. Baseline characteristics are published (1) and shown in Supplementary Table 1. Briefly, the overall study group (58% female, 88% non-Hispanic White) had mean age of 40 years, mean diabetes duration of 23 years, mean HbA_{1c} of 7.8%, and mean BMI of 35 kg/m^2.

In the semaglutide group, TDD decreased significantly from baseline both in absolute units and percentage terms, across all postbaseline time points

($P < 0.001$ for all). In the semaglutide group, the least square mean change in TDD (95% CI) was −12.2 units/day at week 4 (−16.7 to −7.7), −16.0 units/day at week 8 (−20.5 to −11.4), −15.2 units/day at week 20 (−19.8 to −10.7), and −17.4 units/day at week 26 (−22.0 to −12.9) (Fig. 1*A*). These correspond to mean percent (95% CI) reductions of −17.7% (−23.3 to −12.1), −20.9% (−26.4 to −15.3), −19.1% (−24.7 to −13.5), and −22.6% (−28.3 to −17.0), respectively (Fig. 1*B*). In contrast, the placebo group showed no significant change in TDD at weeks 4, 8, or 20. However, by week 26, a statistically significant increase in TDD was observed in the placebo group, with an estimated TDD increase of +5.2 units/day (95% CI 0.7–9.7), corresponding to a 7.1% increase in the TDD from baseline (95% CI 1.5–12.7).

In the semaglutide group, basal and bolus insulin doses were significantly reduced from baseline across all time points, with a greater reduction observed in bolus insulin than in basal insulin. In the semaglutide group, basal insulin (95% CI) decreased −4.7 units/day at week 4 (−7.1 to −2.3), −5.6 at week 8 (−8.0 to −3.2), −4.7 at week 20 (−7.1 to −2.3), and −6.6 at week 26 (−9.1 to −4.2) (Fig. 1*C*). The corresponding percent reductions (95% CI) were −11.7% (−17.4 to −5.9), −12.4% (−18.2 to −6.7), −9.8% (−15.6 to −4.0), and −15.6% (−21.5 to −9.7), respectively (Fig. 1*D*). The bolus insulin dose (95% CI) decreased by −7.5 units/day at week 4 (−10.7 to −4.2), −10.4 at week 8 (−13.7 to −7.2), −10.6 at week 20 (−13.9 to −7.3), and −10.9 at week 26 (−14.2 to −7.5) (Fig. 1*C*), corresponding to percent reductions (95% CI) of −22.9% (−31.8 to −14.1), −29.1% (−38.0 to −20.3), −28.7% (−37.6 to −19.8), and −30.5% (−39.5 to −21.5), respectively (Fig. 1*D*). The basal to total insulin ratio of the placebo group was mean ± SD 0.57 ± 0.02 at baseline and remained similar within 0.56–0.58 at the subsequent time points (P = NS for all). The basal to total insulin ratio for the semaglutide group increased from mean ± SD 0.56 ± 0.02 at baseline to 0.60 ± 0.02 at 4 weeks, 0.62 ± 0.02 at 8 weeks, 0.63 ± 0.02 at 20 weeks, and 0.62 ± 0.02 at 26 weeks ($P < 0.001$ for all). Taken together, the data indicate semaglutide reduced both basal and bolus insulin immediately after initiation, and the reduction in bolus insulin was two- to threefold greater than the reduction in basal insulin.

Insulin dose (in units/kg/day) remained relatively stable in the placebo group across the study period, ranging from 0.70 to 0.76 units/kg/day. In contrast, the semaglutide group exhibited a significant and sustained decline in insulin dose after treatment initiation. From a baseline of 0.72 units/kg/day (95% CI 0.64–0.81), the insulin dose decreased to 0.61 at week 4 (95% CI 0.53–0.69), 0.59 at week 8 (95% CI 0.51–0.67), 0.62 at week 20

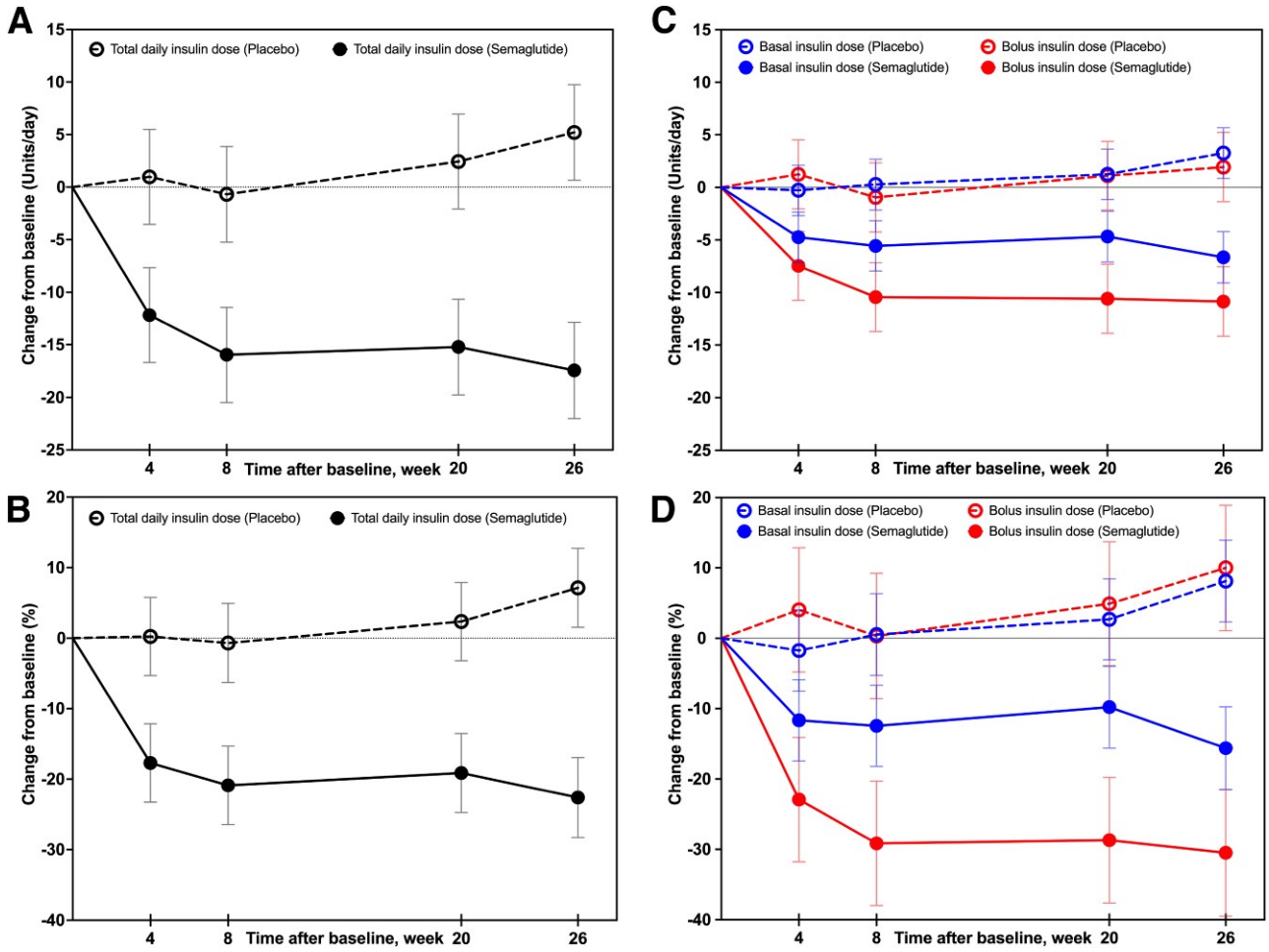

Figure 1—Insulin dose changes from baseline in semaglutide (solid line) and placebo (dashed line) groups. Change in TDD as units/day (*A*) and percentage (*B*). Change in basal (blue lines) and bolus (red lines) insulin doses as units/day (*C*) and percentage (*D*).

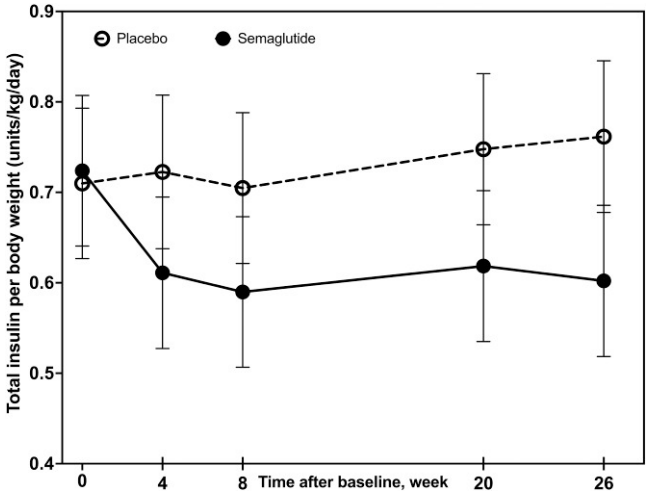

Figure 2—Total insulin per body weight (units/kg/day) in semaglutide (solid line) and placebo (dashed line) groups over time. Data are missing for 11 individuals at 4 weeks, one individual at 20 weeks, and one at 26 weeks.

(95% CI 0.54–0.70), and 0.60 at week 26 (95% CI 0.52–0.69) ($P < 0.001$ for all) (Fig. 2).

Both body weight and TDD decreased after treatment, with the reduction in TDD being more pronounced during the early treatment period. To evaluate the respective contributions of weight loss and direct medication effects, a mediation analysis was performed. At week 4, the difference in TDD between the semaglutide and placebo groups was −13.3 units/day (95% CI −19.4 to −7.5), of which −2.3 units/day (95% CI −4.4 to −0.4) was attributable to weight loss, corresponding to 17% (95% CI 3.5–35) of weight loss. At week 8, the between-group difference (95% CI) increased to −15.0 (−20.5 to −9.6) units/day, with −4.7 (−7.2 to −2.6) units/day explained by weight loss as 31% (17–54). This difference further increased to −18.0 (−23.5 to −12.2) units/day at week 20 and −21.9 (−27.5 to −16.1) units/day at week 26, with weight loss accounting for −9.1 (−12.6 to −5.9) units/day (50%; 95% CI 31–80) and −10.5 (−14.7 to −6.9) units/day (48%; 95% CI 31–73) of the reductions, respectively (Fig. 3). Taken together, semaglutide exerted a direct effect on TDD reduction, consistently ranging from –8.9 to –11.4 units/day between groups, which was most prominent at the beginning of treatment. Over time, weight loss contributed increasingly to the overall between-group difference in TDD, particularly during later stages of semaglutide therapy when relatively higher doses were administered.

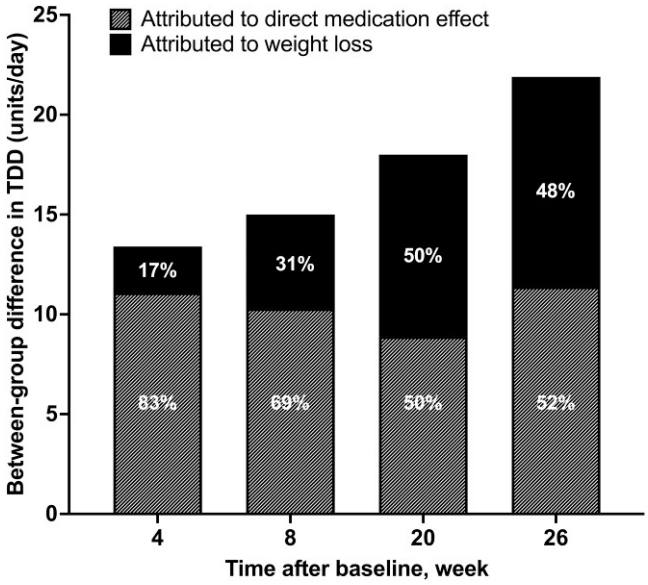

Figure 3—TDD difference between semaglutide and placebo groups at postbaseline time points. TDD difference attributed to weight loss and direct medication effect are shown separately in black and gray, respectively, with the percentage values of distribution.

Carbohydrate amount and the number of user-initiated boluses entered to AID systems were available for 22 individuals in the placebo group and 24 individuals in the semaglutide group. Over 26 weeks, the amount of carbohydrate intake per day decreased in the semaglutide group, whereas it remained stable in the placebo group (Supplementary Fig. 1). Mean carbohydrate intake (95% CI) in the semaglutide group decreased from 137 g/day (107–167) at baseline to 116 g/day (87–147; $P = 0.015$) at 4 weeks, to 99 g/day (69–129; $P < 0.001$) at 8 weeks, to 106 g/day (76–136; $P < 0.001$) at 20 weeks, and to 107 g/day (76–137; $P < 0.001$) at 26 weeks.

Similarly, the number of user-initiated boluses was reduced in the semaglutide group from mean ± SD 4.6 ± 0.4 boluses/day at baseline to 3.9 ± 0.4, 3.8 ± 0.4, 3.6 ± 0.4, and 3.4 ± 0.4 boluses/day ($P < 0.001$ at all time points versus baseline) at 4, 8, 20, and 26 weeks, respectively. In the placebo group, the number of meal boluses remained stable at mean ± SD 4.1 ± 0.4 boluses/day at baseline to 4.4 ± 0.4, 4.2 ± 0.4, 4.4 ± 0.4, and 4.4 ± 0.4 boluses/day (P = NS for all) at 4, 8, 20, and 26 weeks, respectively.

The number of correction boluses delivered by the Tandem Control-IQ and Medtronic systems was reduced slightly in the semaglutide group with mean ± SD 4.3 ± 0.6, 3.4 ± 0.6 ($P = 0.002$), 3.6 ± 0.6 ($P = 0.016$), 4.0 ± 0.6 ($P = 0.225$), and 4.0 ± 0.6 ($P = 0.302$) boluses/day at baseline, at 4, 8, 20, and 26 weeks, respectively. The number remained similar in the placebo group, with mean ± SD 5.3 ± 0.6, 4.6 ± 0.6 ($P = 0.063$), 4.8 ± 0.6 ($P = 0.145$), 5.1 ± 0.6 ($P = 0.626$), and 4.5 ± 0.6 ($P = 0.04$) boluses/day at baseline, 4, 8, 20, and 26 weeks, respectively. Taken together, semaglutide reduced carbohydrate intake and user-initiated boluses within the first month of treatment and this was sustained over time; the AID initiated automated corrections were not affected to the same extent.

CONCLUSIONS

This post hoc analysis of the ADJUST-T1D trial data showed that initiating semaglutide in adults with T1D and obesity had an immediate effect on insulin doses, particularly bolus doses. Within the first month of treatment, the reduction in TDD was mostly independent of weight loss. There was a small reduction in the number of carbohydrates ingested per day by 20 g/day (from 137 g/day at baseline to 116 g/day at week 4). Hence, neither weight loss nor reduction in carbohydrate intake fully explains the reduction in TDD observed (by 20–30%) within first 4 weeks of semaglutide treatment. Moreover, the dose of semaglutide in the first 4 weeks was only 0.25 mg/week.

This observation has important clinical implications. First, an immediate reduction in the bolus insulin (e.g., insulin to carbohydrate ratio, correction factor, and potentially other settings depending on the AID system) by 20–30% is very important with initiation of semaglutide to minimize the risk of hypoglycemia in individuals already receiving adequate insulin therapy. Moreover, the insulin dose reduction was modest after 8 weeks (0.5 mg/week semaglutide); hence, the first 8 weeks appears to be the critical period for insulin adjustment. Second, the weight loss observed during follow-up may necessitate further dose reductions in a weight loss–dependent manner. Because weight loss tends to be more pronounced in the later months of GLP-1RA therapy, more frequent follow-up for insulin dose adjustments based on weight loss may be needed.

Basal insulin delivery in AID systems has two components: the basal insulin required to meet the body's physiological needs, and compensatory adjustments based on predicted glucose trends (e.g., increased basal insulin in response to a missed bolus after a snack) (5–7). The physiological basal insulin requirement may change with alterations in insulin sensitivity or body weight (8). In this study, basal insulin doses decreased within the first month of treatment, a period during which weight loss was minimal. Therefore, the initial reduction in basal insulin is unlikely to be attributed to changes in body weight. The second component (compensatory basal insulin adjustments) typically responds to missed or underestimated bolus doses. In this context, reduced carbohydrate intake and the corresponding lower need for bolus insulin likely lessened the demand for such compensatory increases in basal insulin during the early phase of treatment.

After semaglutide treatment, the reduction in bolus insulin was greater than the reduction in basal insulin doses. This pattern was also reflected in an increased basal dose to TDD ratio. The selective reduction in bolus insulin suggests a decrease in carbohydrate intake, which was further supported by reduced carbohydrate entries into AID systems in the semaglutide group. However, the percent reduction in bolus doses was greater than the reduction in carbohydrate intake; thus, several questions emerge. Previous clamp studies in people with type 2 diabetes have shown that semaglutide treatment increases endogenous insulin secretion and insulin sensitivity (9,10). However, it is unknown how semaglutide affects insulin sensitivity in individuals with T1D. Similarly, the effect of semaglutide on residual c-peptide response is unknown and remains an important direction for research.

Previous studies of semaglutide treatment in adults with T1D and obesity showed varying reductions in TDD. In a randomized controlled trial with adults with T1D who used AID systems, semaglutide treatment up to 1 mg/week reduced TDD by 11.3 units/day compared with placebo, driven by the reduction in bolus insulin (−6.2 units/day) at 15 weeks (11). In another randomized controlled trial, semaglutide up to 1 mg/week over 12 weeks reduced TDD by 8.5 units/day (12). In a real-world study with 50 individuals, TDD was reduced by 4.9 U/day at 3 months and 6.1 units/day at 6 months (13). In another real-world study with 42 individuals, TDD was reduced 8.4 units/day at 6 months (14). The doses of GLP-1RA and type of GLP-1RAs (including gastric inhibitory poeptide [GIP]/GLP-1RA) used in real-world studies were variables making it difficult to ascertain effects of GLP-1RA on insulin dose changes.

GLP-1RA has multiple effects on glycemia, weight, and cardiorenal outcomes, and these also affect each other directly. Other studies also used mediation analyses to reveal the direct and indirect effects of these factors. In the outcome study of semaglutide in adults with type 2 diabetes, the reductions in HbA_{1c} and systolic blood pressure mediated 25% and 22% of the effect on renal protection, respectively; however, weight loss did not. (15). Another mediation analysis of that study showed the higher diabetic retinopathy rates were mediated by the rapid reduction in HbA_{1c} (16). Semaglutide may also reduce high-sensitivity C-reactive protein levels in people with type 2 diabetes, partially mediated by reductions in HbA_{1c} and weight (17). Here, we showed the weight loss–mediated TDD reduction in T1D and obesity.

The carbohydrate amount entered to the AID systems in our study was comparable to those reported in previous studies. In a randomized controlled trial studying carbohydrate counting in adults with T1D, the mean carbohydrate amount entered to the AID systems was mean ± SD 129.9 ± 62 g/day (18). A real-world study with 453 adults with T1D who used AID systems reported 132 ± 80 g/day carbohydrate entry (19). The median (interquartile range) carbohydrate amount entered in AID systems in adults with T1D using semaglutide 1 mg/week was 95 (75–141) g/day, and 142 (100–172) g/day in the placebo group (11).

Although semaglutide reduced both carbohydrate intake and insulin requirements, there were no diabetic ketoacidosis events throughout the study. One hyperglycemia event due to infusion-site failure and one high-ketone event (not meeting diabetic ketoacidosis criteria) were reported in the semaglutide group (1). Severe hypoglycemia events were similar between groups.

To our knowledge, this is the first study to evaluate changes in insulin doses with semaglutide treatment over 26 weeks in adults with T1D and obesity. The double-blind, randomized trial design and collection of data from insulin pumps and CGM are major strengths. However, there are a few limitations worth considering. First, missing carbohydrate entry data for one-third of the participants limited our ability to fully assess changes in carbohydrate intake and could not be incorporated in the mediation analysis. Carbohydrate amounts were collected from AID systems, which may not reflect actual consumption. More importantly, the change in carbohydrate entries over time likely reflects meaningful shifts in participants' dietary behaviors. Second, we used only up to 1 mg of semaglutide; thus, it is difficult to ascertain the effects of higher dose of semaglutide on weight loss and insulin dose reduction in adults with T1D. Third, the reduction in weight did not plateau at

week 26, and there could be a marginal further reduction in weight and TDD with longer treatment duration. Fourth, we did not measure c-peptide levels, which could have provided further insight on effects of semaglutide on endogenous insulin secretion.

In conclusion, semaglutide treatment as an adjunct to AID systems led to an immediate reduction in basal and bolus insulin doses and in carbohydrate intake. These findings support the need for early and proactive insulin dose adjustments, especially for bolus insulin, monitoring of weight changes, and ongoing assessment of insulin needs in individuals with T1D who initiate semaglutide therapy.

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References

1. Shah VN, Akturk HK, Kruger D, et al. Semaglutide in adults with type 1 diabetes and obesity. NEJM Evid 2025;4:EVIDoa2500173
2. Mathieu C, Zinman B, Hemmingsson JU, et al.; ADJUNCT ONE Investigators. Efficacy and safety of liraglutide added to insulin treatment in type 1 diabetes: the ADJUNCT ONE treat-to-target randomized trial. Diabetes Care 2016;39:1702–1710
3. Ahrén B, Hirsch IB, Pieber TR, et al.; ADJUNCT TWO Investigators. Efficacy and safety of liraglutide added to capped insulin treatment in subjects with type 1 diabetes: the ADJUNCT TWO randomized trial. Diabetes Care 2016;39:1693–1701
4. Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. mediation: R package for causal mediation analysis. J Stat Soft 2014;59:1–38
5. Messer LH, Breton MD. Therapy settings associated with optimal outcomes for t:slim X2 with Control-IQ technology in real-world clinical care. Diabetes Technol Ther 2023;25:877–882
6. Minsky N, Shalit R, Benedetti A, et al. Simplified meal management in adults using an advanced hybrid closed-loop system. Diabetes Technol Ther 2025;27:27–33
7. Renard E, Weinstock RS, Aleppo G, et al.; OP5-003 Research Group. Efficacy and safety of a tubeless AID system compared with pump therapy with CGM in the treatment of type 1 diabetes in adults with suboptimal glycemia: a randomized, parallel-group clinical trial. Diabetes Care 2024;47:2248–2257
8. Mitsui Y, Kuroda A, Ishizu M, et al. Basal insulin requirement in patients with type 1 diabetes depends on the age and body mass index. J Diabetes Investig 2022;13:292–298
9. Heise T, Mari A, DeVries JH, et al. Effects of subcutaneous tirzepatide versus placebo or semaglutide on pancreatic islet function and insulin sensitivity in adults with type 2 diabetes: a multicentre, randomised, double-blind, parallel-arm, phase 1 clinical trial. Lancet Diabetes Endocrinol 2022;10:418–429
10. Mather KJ, Mari A, Heise T, et al. Effects of tirzepatide vs semaglutide on β-cell function, insulin sensitivity, and glucose control during a meal test. J Clin Endocrinol Metab 2024;109:3046–3054
11. Pasqua M-R, Tsoukas MA, Kobayati A, Aboznadah W, Jafar A, Haidar A. Subcutaneous weekly semaglutide with automated insulin delivery in type 1 diabetes: a double-blind, randomized, crossover trial. Nat Med 2025;31:1239–1245
12. Navodnik MP, Janež A, Žuran I. The effect of additional treatment with empagliflozin or semaglutide on endothelial function and arterial stiffness in subjects with type 1 diabetes mellitus–ENDIS study. Pharmaceutics 2023;15:1945
13. Snell-Bergeon JK, Kaur G, Renner D, Akturk HK, Beatson C, Garg SK. Effectiveness of semaglutide and tirzepatide in overweight and obese adults with type 1 diabetes. Diabetes Technol Ther 2025;27:1–9
14. Mertens J, De Winter HT, Dirinck E, Francque S, De Block C. Real-world evidence of the effect of adjunctive semaglutide on weight change, glycemic control, and metabolic dysfunction-associated steatotic liver disease in people with type 1 diabetes. Diabetes Technol Ther. 24 July 2025 [Epub ahead of print]. DOI: 10.1177/15209156251362497
15. Mann JFE, Buse JB, Idorn T, et al. Potential kidney protection with liraglutide and semaglutide: exploratory mediation analysis. Diabetes Obes Metab 2021;23:2058–2066
16. Vilsbøll T, Bain SC, Leiter LA, et al. Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. Diabetes Obes Metab 2018;20:889–897
17. Mosenzon O, Capehorn MS, De Remigis A, Rasmussen S, Weimers P, Rosenstock J. Impact of semaglutide on high-sensitivity C-reactive protein: exploratory patient-level analyses of SUSTAIN and PIONEER randomized clinical trials. Cardiovasc Diabetol 2022;21:172
18. Haidar A, Legault L, Raffray M, et al. A randomized crossover trial to compare automated insulin delivery (the artificial pancreas) with carbohydrate counting or simplified qualitative meal-size estimation in type 1 diabetes. Diabetes Care 2023;46:1372–1378
19. Godard E, Penfornis A, Amadou C. Long-term patterns in automated insulin delivery and carbohydrate announcement: a 24-month follow-up. Diabetes Technol Ther. 23 July 2025 [Epub ahead of print]. DOI:10.1177/15209156251362499