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Update on the role of GLP-1 receptor agonists in people with type 1 diabetes mellitus

I will start with a question: do you know someone with type 1 diabetes mellitus (T1DM) who is overweight and unable to reduce it despite multiple attempts, and who needs high doses of insulin to control glucose?

Drugs known as *glucagon-like peptide-1* receptor agonists (GLP-1 RAs) currently marketed (liraglutide, dulaglutide, and semaglutide) and the more recent dual agonist of *glucagon-like peptide-1* and *gastric inhibitory polypeptide receptors* (GLP-1/GIP RA) marketed (tirzepatide) have demonstrated a fundamental role not only in glucose control in people with type 2 diabetes mellitus (T2DM), but also in weight reduction in people with and without T2DM with obesity or overweight, and in reducing cardiovascular and renal morbidity and mortality in people with T2DM and cardiovascular or renal disease (1). For this reason, they are extremely interesting and attractive molecules to also use in people with T1DM. **However, at present their use in T1DM is not authorized in the product label due to the lack of scientific studies with sufficient statistical power to support it**. Fortunately, we do have some scientific studies that give us "clues" about the role they could play in the treatment of people with T1DM.

The obesity-diabetes pair has traditionally been considered a problem linked to people with T2DM. Historically, people with T1DM did not present obesity, and the objective of studies and treatment was almost exclusively glucose control. »

» For several decades this has no longer been the case, and **from the age of 18 approximately 30% of people with T1DM are overweight and between 16–30% have obesity** (1). In general, the prevalence of obesity in people with T1DM is similar to the prevalence of obesity in the general population of that country or region. Obesity per se, regardless of whether diabetes is present or not, is associated with insulin resistance, dyslipidemia, hypertension, heart disease, sleep apnea, osteoarticular degeneration, and some types of cancer. It is important toOf note, that people with T1DM, even without excess weight, due to the need to administer insulin in the subcutaneous tissue, already present hyperinsulinemia in peripheral blood and insulin resistance (in muscle and blood vessels and probably also in liver and adipose tissue), which may be related, at least partially, to increased cardiovascular morbidity and mortality (2). Thus, the treatment management of people with T1DM must be comprehensive and, together with adequate glycemic, lipid, and blood pressure control, combating overweight and obesity is an objective of vital importance.

No one disputes that to achieve a healthy weight it is essential to maintain a healthy diet and be physically active while avoiding sedentary behavior, but for people with T1DM receiving on intensive treatment "have it moreeverything is a little difficultharder". Intensification of treatment is associated with weight gain and with the intake of carbohydrates to combat and/or prevent hypoglycemia (which increases weight). People with T1DM do not live in a bubble, and the same social and environmental stimuli that cause obesity in society in general obviously also affect them. In addition, fear of experiencing hypoglycemia during exercise is also associated with reduced physical activity. None of this helps people with T1DM avoid excess weight. Given the growing popularity of semaglutide and tirzepatide as drugs for the treatment of obesity in people without diabetes, it is almost inevitable to ask whether people with T1DM and excess weight could also benefit from their use.

In 2016 the ADJUNCT ONE (3) and ADJUNCT TWO (4) studies were published, two large placebo-controlled clinical trials in which liraglutide was used as adjunct therapy to insulin with the main objective of evaluating whether it could help improve metabolic control in people with T1DM. The reduction in HbA1c ranged from 0.3 to 0.49% (the difference fading after one year of use), but with a significant increase in the occurrence of ketosis and hypoglycemia. There wFurthermore, there was also a reduction in body weight of 1.2 to 4 kg (the higher the dose of liraglutide, the greater the weight loss) and a reduction in total insulin dose of 3 to 10% compared withvs baseline. Overall, the results were somewhat modest and dampened interest in the use and investigation of liraglutide in people with T1DM.

More recent and more frequent approaches in studies using semaglutide or tirzepatide in people with T1DM no longer evaluate them as insulin adjuncts to improve metabolic control, but rather as drugs for weight loss, with improvement of glycemic control often becoming a secondary objective. The strictly glucocentric vision of treating people with T1DM is thus broadened to address excess weight, insulin resistance, and hyperinsulinism. Although these studies are not designed to determine whether cardiovascular risk is reduced, it seems plausible that this could occur if weight reduction were achieved in an effective and safe manner. Fortunately, a clinical trial is underway to answer this question: NCT05819138: Type 1 Diabetes Impacts of Semaglutide on Cardiovascular Outcomes. Another trial is evaluating renal benefit: NCT05822609: Trial of Semaglutide for Diabetic Kidney Disease in Type 1 Diabetes. However, we will still have to wait for the results to be published.

Until 2024 we did not have studies using these molecules that were not almost anecdotal due to the small number of patients included. That year, Barbara Davis Hospital in Colorado published the first retrospective real-world study using semaglutide at a dose in most patients equal to or less than 1 mg/week (5). Shortly afterward, a second retrospective real-world study was published using tirzepatide at a dose in most patients of 10 mg/week (6). Both studies involved people with T1DM and overweight or obesity, all using continuous glucose monitoring (CGM), and insulin administered either as multiple daily injections or via insulin pumps. **People with T1DM treated with semaglutide achieved after one year an average weight loss of 7.2 kg**, equivalent to a 7.6% reduction in body weight, compared with vs a 1 kg increase (1%) in the control group. »

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There were no significant changes in HbA1c or insulin dose, although there was an **increase in time in range** (time with glucose between 70–180 mg/dL) **of 5%** and a reduction in glycemic variability measured by the coefficient of variation. People treated with tirzepatide after one year reduced body weight by an average of 21 kg, equivalent to 18.5% of body weight, compared withvs no change in the control group. They also reduced HbA1c by 0.62% and the daily insulin dose by 0.33 IU/kg compared withvs the control group. **Time in range** also improved with an increase of almost **10%**, along with a reduction in glycemic variability, although after one year the improvement did not reach statistical significance. The most frequent adverse effects, as expected, were mild to moderate gastrointestinal symptoms, with no episodes of severe hypoglycemia or diabetic ketoacidosis.

Insulin administration **through hybrid closed-loop systems** (HCLS), in which the insulin pump is integrated with a CGM system through an algorithm, is the most effective and safest way to control diabetes in people with T1DM. Even with these

» systems, controlling postprandial glucose remains a challenge. In the 26-week multicenter randomized prospective ADJUST-T1D study (7), semaglutide was used at increasing doses up to 1 mg/week in people already using an HCLS. Thirty-six percentA total of 36% of people receiving semaglutide, compared wi thvs 0% receiving placebo, achieved the primary endpoint of > 70% time in range together with < 4% time with glucose < 70 mg/dL (hypoglycemia) and **at least a 5% reduction in body weight**. There were no differences in episodes of severe hypoglycemia or diabetic ketoacidosis. The insulin dose per kg of body weight remained stable in the placebo group and progressively decreased in the semaglutide group from an initial mean daily dose of 0.72 IU/kg to 0.6 IU/kg after 26 weeks. Both basal and bolus insulin doses were reduced, but bolus insulin was reduced two to three times more than basal insulin (8). Therefore, to avoid hypoglycemia, it is important to **program HCLS systems by reducing bolus insulin by approximately 30%** compared withvs the dose programmed before starting semaglutide. Results consistent with this study have also been observed in another smaller prospective crossover study in which patients served as their own controls (9). **Tirzepatide** at a dose of 5 mg, in the TIRT-LE1 study (10), a 12-week randomized placebo-controlled prospective study, produced an average difference in **weight loss of 8.7 kg**, equivalent to an 8.8% reduction in body weight. Fat mass decreased by 7.2 kg, and the total daily **insulin dose was reduced by 35%**, equivalent to a reduction of 29% in daily insulin dose per kg. There were no significant changes in CGM glucose metrics or HbA1c. People treated with tirzepatide did not experience episodes of severe hypoglycemia or ketoacidosis.

We do not yet know whether the weight reduction achieved with these molecules will be comparable to that seen in populations without diabetes or in people with T2DM, or whether it will differ, as the studies include relatively few participants and are not very long in duration. However, these are undoubtedly encouraging results and support further exploration of the benefits of these molecules in people with T1DM.p D

CONCLUSIONS

- People with T1DM have excess weight with a prevalence similar to that of people without diabetes in the same country or region.
- Obesity per se, regardless of whether diabetes is present, is associated with insulin resistance, dyslipidemia, hypertension, heart disease, sleep apnea, osteoarticular degeneration, and some types of cancer.
- Semaglutide and tirzepatide may have a role in weight reduction in people with T1DM and obesity or overweight, although at present there are few studies available.
- To avoid hypoglycemia, it is recommended to reduce the previous insulin dose.

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