Questions From ADA and ENDO Symposia Participants

Weight Management

Should we focus on total weight loss or excess weight loss to improve outcomes?

Percent of weight loss is preferred in clinical trials and for standardization of terms. Dividing excess weight loss by two gives the total weight loss. The most important thing is for the patients to lose weight in terms of excess abnormal ectopic body fat.

The focus should be on total weight loss. In clinical trials of non-surgical therapies for overweight and obesity, total weight loss (not excess weight loss) is almost exclusively used when reporting outcomes. The weight loss is generally reported as a percent weight loss of the baseline body weight and clinical benefits of weight reduction are linked to this percent weight loss from baseline.

How do you recommend calculating the correct % body weight loss for each patient?

This should be individualized and should be a shared decision with the patient. Factors that should be taken into consideration include the patient's wishes, co-morbidities associated with obesity, age, and degree of frailty (if any), etc. Clinically significant health benefits can be seen with greater than 3%-5% body weight reduction and are progressive, with greater benefit seen with progressively greater weight loss.

How should we decide between A1c control vs weight loss for T2D management?

Both are very important and are interrelated. In patients with diabetes, we should aim to improve glycemic control to an individualized A1c target. This is primarily done to avoid symptoms of hyperglycemia and to reduce the risk of microvascular and macrovascular disease. Reduction in body weight generally leads to an improvement in A1c. Importantly, reduction in body weight also addresses the common complications/co-morbidities of obesity, including hypertension, dyslipidemia, fatty liver disease, sleep apnea, etc. We are fortunate to have agents today that address both A1c and body weight, and we should address them both simultaneously when necessary and possible.

Fatty liver is on the rise with the epidemic of obesity, and it is becoming a leading cause of nonalcoholic hepatic steatosis and liver failure. Is there a certain % weight loss that reduces fatty liver infiltration?

Yes. Well-conducted trials have assessed this, and in general ≥3% body weight loss is associated with improvement in hepatic steatosis (liver fat), ≥5% weight loss is associated with improvements in inflammation and ballooning (hepatocyte damage), ≥10% wight loss is associated with NASH resolution, and ≥15% weight loss is associated with improvement in fibrosis in many patients. The greater the degree of weight loss, the greater the benefit. Reference: Vilar-Gomez E et al. *Gastroenterology*. 2015;149:367–378.

Incretins, GIP, Dual Agonism

Is there downregulation from stimulating GIP receptors?

Decreased expression of GIPR upon exposure to very high concentrations of GIP has been demonstrated in cultured cells and rodent models in response to hyperglycemia.

What are the effects of incretins on glucagon? Does this change with T2D?

GLP-1 reduces glucagon concentrations in diabetic and nondiabetic humans. It is unclear whether this is a direct or indirect effect of GLP-1 on α cells, but most people think it is the latter, and that it probably involves somatostatin release from Δ cells stimulated by GLP-1. GIP stimulates glucagon release in diabetic and nondiabetic humans. The GIPR is expressed by α cells and the effect of GIP is likely direct. The effect is greatest at low plasma glucose concentrations and becomes negligible at hyperglycemia.

What are your thoughts on GIP antagonism also leading to weight loss?

This story builds on old studies demonstrating that GIP (usually in concert with insulin) increases glucose uptake and lipogenesis in cultures of adipose tissue and fat explants. Data with GIPR pharmacology has been questioned because of variable characterization of antagonists. Studies with GIPR knockout mice have been overinterpreted. There is no clearly delineated mechanism by which GIPR antagonists lead to weight loss.

How does a combined GLP/GIP analog compare with a combined GLP/glucagon agonist?

It seems likely that there would be different actions, but there have been few direct comparisons in preclinical models and none in humans. Theoretically, GIPR/GLP-1R agonism should have its strength in improving glycemia, and GLP-1R/glucagon-R perhaps in weight loss, as glucagon enhances energy expenditure.

As dual action medications have less specific attachment to GLP-1 receptor, what about using a GLP-1 agonist and twincretin at the same time?

The in vivo activity of incretins (mono or multi-receptor agonists) at the GLP-1R is not well characterized. Extension of in vitro receptor pharmacology to clinical medicine should be done cautiously, and any benefit would have to be established with clinical trials. Based on current knowledge, this doesn't appear to be the way to go.

Does GIP affect β-cell mass and/or apoptosis? With dual stimulation, is there β-cell apoptosis?

There is evidence from studies of cultured β cells in mice that GIP has some beneficial effects to reduce apoptosis and possibly stimulate cell growth. Caution should be applied when extending these effects to humans. β-cell growth and regression is much more dynamic in rodents, and long-term effects of GLP-1RA on functional measures of β-cell mass have been paltry to date. Even with GLP-1R agonists, β-cell proliferation is only observed in young animals. In humans β-cells have the propensity to proliferate only during certain periods: during infancy, in puberty, and in pregnant women. Outside these windows of opportunity, no β-cell proliferation has ever been observed with either GLP-1R or GIPR agonists.

What happens to GIP levels after bariatric surgery, and does it contribute to neisidioblastosis seen in these patients?

On the whole most studies report similar or just slightly elevated GIP secretion after gastric bypass or sleeve gastrectomy. It is highly questionable whether nesidioblastosis occurs at all after bariatric surgery, but it seems unlikely that GIP would be involved in any abnormal β-cell growth under these circumstances.

Is there any benefit of using a GLP-1RA in patients with a history of pancreatectomy?

There is very little data so support this. There are trials of GLP-1RA in people with T1D who are also insulinopenic. In this group there is a modest (0.4%-0.6%) reduction in A1c and weight loss with small reductions in total daily insulin dose (which might increase the risk of ketoacidosis during sick days). Most patients with pancreatectomy are underweight and the benefits of GLP-1RA seem very limited.

Does the gila monster make GIP and does it have a similar function as in humans?

Lizards make GIP. Most likely, it is an intestinal peptide like in mammals, while exendin-4 is found in the saliva of these animals. Since they feed only 2-3 times a year, exendin-4 in the saliva may be a signal triggering proliferation of intestinal mucosal cells, which undergo atrophy between feedings.

Tirzepatide MOA

To know the effect of GIP agonism with tirzepatide, why not conduct a knockout study for GLP and GIP receptors?

The knockout study has been done and showed a reduced effect in animals with knockout of either the GIP or GLP-1 receptor. Therefore, it has been proven that it interacts with both receptors and only gives the full response when both receptors and the signaling pathways are intact.

Which component of tirzepatide (GIP or GLP-1) produces more weight loss?

This is not yet known. Based on results of preclinical studies and the finding of GIP receptors in areas of the brain that are important for energy balance, both GIP and GLP-1 agonism most likely contribute to the weight loss, but the relative contribution of each is not known.

What percentage of weight loss and A1c reduction from tirzepatide come from GIP?

The precise relative contribution of GIP and GLP-1 receptor agonism to tirzepatide-induced weight loss and glucose reduction are not known. They are both thought to contribute to these effects, but the degree to which agonism of each receptor leads to these improvements is not known.

Could GIP be prolonging the GLP-1 exposure window due to satiety that was previously limited by nausea?

Yes, this is a possibility. GIP has experimentally been shown to reduce nausea via binding to central receptors. Theoretically this activity could widen the therapeutic window of GLP-1 receptor agonism, which can be limited by nausea.

Tirzepatide Efficacy

What's the etiology of the difference in average weight loss between T2D patients and non-diabetic patients?

The reasons for this are likely multifactorial. In patients with very poor glycemic control, agents that improve glycemic control also reduce loss of calories secondary to glucosuria (loss or glucose [calories] in the urine). Also, often patients with T2D are on antihyperglycemic agents that promote weight gain. These agents, such as insulin, sulfonylureas, and thiazolidinediones, may reduce lifestyle and/or medication-induced weight loss. Additionally, there may resistance to pharmacotherapy in patients with T2D (versus individuals without diabetes) resulting in less weight reduction in this patient population.

During weight loss with tirzepatide, what was different in the diet? Skipped meals? Skipped snacks? Smaller meals? Does appetite increase on day 6?

The mechanisms associated with food intake, energy expenditure, and micronutrient intake are currently unknown. The studies demonstrated that tirzepatide reduces hunger, increases satiety, and reduces susceptibility to high-reward eating.

How long does it take to achieve the weight reduction goal in individual patients?

Higher weight loss was observed in 52-week studies than in those lasting 40 weeks. In SURPASS-2 weight loss continued beyond 40 weeks. In SURPASS-3, weight loss did not plateau at 52 weeks with 10 mg and 15 mg tirzepatide doses. In SURPASS-4, the weight loss plateau was observed between 52 and 60 weeks.

Are there renal benefits with tirzepatide?

There are no studies specifically assessing the effect of tirzepatide on renal function. A recently presented pre-specified exploratory analysis of SURPASS-4 (tirzepatide versus insulin glargine in patients with T2D with high CV risk on up to 3 oral agents) reported that tirzepatide compared with insulin glargine reduced albuminuria and slowed the rate of eGFR decline over time. (Reference: Heerspink H, et al. Oral presentation. American Diabetes Association - 82nd Annual Scientific Sessions; New Orleans, LA, USA; June 3–7, 2022.)

Is tirzepatide less effective with poorer blood sugar control?

As with any antidiabetic agent, the absolute reduction in A1c is greater in patients with poorer glycemic control (higher A1c). In clinical trials, tirzepatide was effective in improving glycemic control and helping patients achieve clinically relevant A1c targets regardless of baseline A1c.

Did the SURPASS trials include moderate and/or intense lifestyle modifications?

SURPASS trials included moderate lifestyle modifications.

Tirzepatide Safety, Precautions, and Contraindications

What proportion of patients stopped taking tirzepatide during SURPASS-2?

In SURPASS-2, 6.0%, 8.5%, and 8.5% of patients treated with tirzepatide 5 mg, 10 mg, and 15 mg, respectively, discontinued tirzepatide because of AEs; 4.1% of patients discontinued semaglutide 1 mg because of AEs.

How long do you expect AEs to last?

This will vary by individual, but in clinical trials, as with selective GLP-1 RAs such as semaglutide and dulaglutide, gastrointestinal AEs with tirzepatide were usually transient and self-limited.

Are AEs worse in any type of patient?

This has not been assessed. The potential for gastrointestinal AEs and strategies for mitigating these events should be discussed with all patients.

What specific counseling do you provide regarding gastrointestinal side effects?

As with selective GLP-1RAs, it is important to proactively tell patients that they may experience gastrointestinal side effects and that these can generally be mitigated with dietary interventions and are generally self-limited and dissipate with time. In clinical trials, if patients taking tirzepatide experienced gastrointestinal side effects, they tended to occur early in the course of therapy (during dose escalation), be mild or moderate in severity, and resolve over time. Relatively few patients had to stop tirzepatide because of gastrointestinal side effects. For example, in a pooled analysis of placebo-controlled clinical trials, discontinuation of treatment because of gas-trointestinal side effects occurred in 3.0%, 5.4%, 6.6%, and 0.4% in patients treated with tirzepatide 5 mg, 10 mg, 15 mg, and placebo, respectively.

How would you start tirzepatide in a patient with a history of or active cholelithiasis?

GLP-1RA trials and post marketing studies have reported acute gall bladder disease such as cholelithiasis or cholecystitis. In the event cholelithiasis is suspected, patients should have appropriate clinical follow-up and diagnostic studies.

Can one justify using tirzepatide rather than a GLP-1RA in a patient with atherosclerotic cardiovascular disease (ASCVD)?

If a selective GLP-1 RA is going to be used for ASCVD risk reduction, one with proven CV benefit should be used. Tirzepatide has been shown to be safe from a CV perspective (SURPASS-4 and a prespecified meta-analysis of 7 randomized controlled trials) but the SURPASS CV outcomes trial (versus dulaglutide) is ongoing and data are expected in 2024.

Was there hypoglycemia seen in studies with tirzepatide in patients without diabetes?

In a recent publication of results of SURMOUNT 1, a randomized controlled trial in persons with overweight or obesity (without diabetes), hypoglycemia <54 mg/dL occurred in 1.4%, 1.6%, 1.6% and 0.2% of participants with 5 mg, 10 mg, 15 mg, and placebo, respectively, during the 72-week trial. No episodes of severe hypoglycemia (requiring assistance of a third party for treatment) were reported.

Taking into account the faster reduction in A1c, are there data related to risk of retinopathy? Were patients with retinopathy excluded from the trials?

The tirzepatide label contains a warning/precaution related to retinopathy. It states that tirzepatide has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Patients with a history of diabetic retinopathy should be monitored for progression because of the well-known finding that rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Patients should follow the standard of care with respect to diabetic retinopathy screening and follow-up and, as standard in clinical practice, should be monitored for progression of retinopathy. Patients should be informed to contact their healthcare provider if changes in vision are experienced during treatment with tirzepatide.

Did de novo retinopathy resolve?

Currently, there are no data on the resolution of de novo retinopathy. Patients should contact their healthcare provider if changes in vision are experienced during treatment with tirzepatide.

Tirzepatide Initiation and Dosing

If a patient gets to the A1c goal on 5 mg of tirzepatide but you want more weight loss, do you increase the dose to 10 mg? Do you worry about hypoglycemia at that point?

The tirzepatide label states that escalation of the dose should be based on glycemic control. Based on the label, in patients with adequate glycemic control on the 5 mg dose, there would be no need to escalate the dose further. Clinical judgment should be used with each patient, based on their individual goals and their comorbidities when making decisions like these in the clinic.

Can you use tirzepatide for those with low C peptide but with obesity?

Yes, tirzepatide can be used for those with low C peptide but with obesity.

Why is there a concern with up titrating the dose for women taking an oral contraceptive?

The label states that women on oral contraceptives should switch or a non-oral method, or add a barrier method of contraception, for 4 weeks after initiation and for 4 weeks after each dose escalation. The reason for this is that slowing of gastric emptying that can occur with the initiation of tirzepatide and after dose escalation can affect the pharmacokinetics of oral contraceptives and may make them less effective. The effect of tirzepatide on gastric emptying is thought to be temporary, which is why the recommendation is to change the method(s) of contraception for 4 weeks after initiation and dose escalation.

Switching to Tirzepatide; Combination Therapy

Would you stop sitagliptin when starting tirzepatide?

Yes. As when starting a selective GLP-1 receptor agonist, when starting a dual GIP and GLP-1 receptor agonist a DPP4 inhibitor (eg, sitagliptin) should be discontinued.

When should you stop glimepiride after you start the tirzepatide?

This should be individualized based on the patient's glycemic control, risk of hypoglycemia, and other factors. Since the reduction in glucose levels was seen relatively quickly upon initiation of tirzepatide (at 4 weeks) and there is an increased risk of hypoglycemia with the use of tirzepatide in sulfonylurea-treated patients, reducing the dose or stopping the sulfonylurea should be considered upon initiation of tirzepatide. This has not been formally assessed in a clinical trial, so clinical judgement should be used.

How do patients already on dulaglutide or semaglutide tolerate tirzepatide?

This has not been assessed in a clinical trial and there is no clinical experience to date. Per the label, tirzepatide should be initiated at the 2.5 mg dose once weekly for 4 weeks and then escalated to 5 mg once weekly. As it is not known how patients will tolerate tirzepatide, the potential for gastrointestinal and other important AEs should be discussed with a patient previously on a selective GLP-1 receptor agonist, just as it is discussed with patients on other background therapies.

When a patient is successful with a dual GLP/GIP agonist, would you first wean off a sulfonylurea or insulin?

Given the increased risk of insulin- and sulfonylurea-induced hypoglycemia when tirzepatide is initiated in patients using these agents, consideration should be given to at least reducing the dose of the sulfonylurea and/or insulin to mitigate the risk of hypoglycemia. This should be individualized on a patient-by-patient basis, and all patients should be reminded of the symptoms and treatment of hypoglycemia. Patients should measure their glucose concentrations at home.

Tirzepatide Approval

How did tirzepatide get FDA approval without having at least non-inferiority on CV outcomes?

Tirzepatide did demonstrate CV safety in the SURPASS-4 trial as well as a prespecified meta-analysis of 7 randomized controlled trials of at least 26 weeks duration. (References: Del Prato S, et al. *Lancet*. 2021;398:1811-1824 and Sattar N, et al. *Nat Med.* 2022;28:591-598.)

Responses courtesy of Dr Juan Pablo Frias, Velocity Clinical Research, Los Angeles, CA; Dr David A. D'Alessio, Duke University, Durham, NC; and Dr Michael A. Nauck, Ruhr University, Bochum, Germany