Dr. Gabriel Cuatrecasas.
Family Doctor, EAP Sarrià, Barcelona.
Coordinator, CAMFIC Obesity Working Group.
PCDE Obesity delegate.

Diabetes and Obesity: beyond BMI

1. INTRODUCTION

Obesity and type 2 diabetes mellitus (T2DM) are two of the leading health epidemics in the modern world. For decades, body mass index (BMI) has been used as a tool to estimate the metabolic risk in individuals with excess weight. However, the »

» relationship between obesity and diabetes goes far beyond a simple number that does not take into consideration the composition or distribution of that body weight.

Among the key structures involved is adipose tissue, which plays a central role in metabolic dysfunction. This dysfunction leads to insulin resistance, eventually progressing to diabetes in many cases (1). As fat tissue grows and becomes unhealthy, it causes systemic changes that impact crucial organs such as the liver, pancreas, skeletal muscle, and cardiovascular system.

Excess adipose tissue not only promotes T2DM but also worsens its effects, accelerating the deterioration of essential organs. In turn, high insulin levels due to resistance promote lipogenesis (fat creation) and fat accumulation, especially in visceral adipose tissue.

This creates a vicious cycle between both conditions, ultimately leading to severe complications like kidney disease, atherosclerosis, arterial ischemia, and heart failure, among others.

2. THE ROLE OF ADIPOSE TISSUE IN INSULIN RESISTANCE

Adipose tissue is a highly active endocrine organ that regulates metabolism by secreting hormones and inflammatory mediators (2). In an obese person, excess fat tissue undergoes a pathological transformation characterized by:

- **Adipocyte Hypertrophy and Hyperplasia:** Under normal conditions, adipocytes store energy as triglycerides. However, when the amount of accumulated fat exceeds the adipose tissue's capacity, adipocytes grow excessively (hypertrophy) or new adipocytes are generated (hyperplasia).
- **Low-Grade Chronic Inflammation:** Obesity is associated with increased production of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These interfere with insulin signaling, promoting insulin resistance.
- **Excessive Lipolysis and Lipid Accumulation in Non-Adipose Organs:** Unhealthy adipose tissue releases a large amount of free fatty acids into the bloodstream. These then deposit in organs like the liver, pancreas, and skeletal muscle, causing dysfunction in these tissues.

3. THE RESTORATION OF THE INCRETIN MECHANISM: A KEY PIECE OF THE PUZZLE

Incretins, primarily glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are hormones secreted by the intestine in response to food intake. These hormones play a fundamental role in glucose regulation by stimulating insulin secretion in a blood glucose-dependent manner, which helps maintain stable blood sugar. Additionally, GLP-1 inhibits glucagon secretion, reducing hepatic glucose production.

Regarding adiposity, incretins also influence energy homeostasis by modulating fat storage. GIP promotes lipid accumulation in adipocytes, while GLP-1 improves insulin sensitivity and reduces caloric intake. Furthermore, incretins play a protective role by improving hepatic insulin sensitivity and reducing hepatic lipogenesis.

The control of hunger and satiety is also closely related to incretin action. They act on the central nervous system, especially in the hypothalamus and brainstem, promoting feelings of fullness and reducing food intake. They also slow down how quickly food moves from the stomach to the small intestine, which prolongs satiety and reduces caloric intake.

Overall, incretin regulation plays an essential role in glycemic homeostasis and body weight control. This has led to the development of incretin-based drugs for treating T2DM and obesity, where an impairment in their function underlies the conditions. These drugs correct the overall metabolic profile (3).

Currently, in Spain, we have several options in this category:

- Liraglutide
- Dulaglutide
- Semaglutide

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EXCESS ADIPOSE TISSUE NOT ONLY PROMOTES T2DM BUT ALSO WORSENS ITS EFFECTS, ACCELERATING THE DETERIORATION OF ORGANS ESSENTIAL FOR THE INDIVIDUAL

» • Tirzepatide

While all have shown benefits in glycemic control and weight reduction, Semaglutide and Tirzepatide show the highest efficacy in both areas, making them considered first-line options for patients with obesity and T2DM.

COMPARISON BETWEEN THE MAIN INCRETIN TREATMENTS (4, 5)

1. Liraglutide

- Daily administration.
- Moderate weight reduction (~5-7%).
- Demonstrated cardiovascular benefit.

2. Dulaglutide

- Weekly subcutaneous administration.
- Weight reduction similar to liraglutide.
- Also demonstrated cardiovascular protection.

3. Semaglutide

- Available in weekly subcutaneous and oral formulations.
- Greater weight reduction (~10-15%).
- More effective reduction in glycated hemoglobin (HbA1c) than liraglutide and dulaglutide.

4. Tirzepatide (GLP-1/GIP dual agonist)

- Acts on two incretin pathways (GLP-1 and GIP).
- Superior weight reduction compared to semaglutide (~15-20%).
- Greater HbA1c reduction, allowing for more effective glycemic control.

CLINICAL IMPACT

Several clinical studies have shown that semaglutide and tirzepatide offer weight reductions close to those achieved with bariatric surgery in some severely obese patients. The use of these treatments not only improves glycemic control and weight reduction but has also demonstrated additional benefits such as:

- Decreased cardiovascular risk in patients with diabetes and obesity.
- Reduced progression of diabetic kidney disease.
- Improved patient functionality and quality of life. D

COMPARATIVE TABLE

TREATMENT	ADMINISTRATION	WEIGHT LOSS REDUCTION	EFFICACY IN HbA1c	CLINICAL IMPACT
Liraglutide	Daily	~5–7%	Moderate	Cardiovascular benefits.
Dulaglutide	Weekly (subcutaneous)	~5–7%	Moderate	Cardiovascular benefits.
Semaglutide	Weekly (subcutaneous) and oral	~10–15%	High	Weight loss close to bariatric surgery, cardiovascular benefits, reduced progression of diabetic kidney disease, improved quality of life.
Tirzepatide	Weekly (subcutaneous)	~15–20%	Very high	Weight loss close to bariatric surgery, cardiovascular benefits, improved quality of life.

Table 1.

CONCLUSIONS

Obesity and T2DM are tightly interconnected diseases. Unhealthy adipose tissue plays a central role in the onset and progression of insulin resistance, affecting multiple key organs.

Latest-generation incretin treatments have proven to be a fundamental tool in managing these conditions, especially Semaglutide and Tirzepatide, which offer superior glycemic control and significant weight loss. These therapies not only address hyperglycemia but also improve the overall metabolic profile and reduce the risk of cardiovascular and renal complications, representing a first-line therapeutic strategy in the fight against obesity and T2DM.

REFERENCES:

1. Lingvay I, Sumithran P, Cohen RV, le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. Lancet. 2022 Jan 22;399(10322):394-405.
2. Busebee B, Ghusn W, Cifuentes L, Acosta A. Obesity: A Review of Pathophysiology and Classification. Mayo Clin Proc. 2023 Dec;98(12):1842-1857
3. Bailey CJ, Flatt PR, Conlon JM. An update on peptide-based therapies for type 2 diabetes and obesity. Peptides. 2023 Mar;161:170939. doi: 10.1016/j.peptides.2023.170939.
4. Xie Z, Hu J, Gu H, Li M, Chen J. Comparison of the efficacy and safety of 10 glucagon-like peptide-1 receptor agonists as add-on to metformin in patients with type 2 diabetes: a systematic review. Front Endocrinol (Lausanne). 2023 Aug 28;14:1244432. doi: 10.3389/fendo.2023.1244432. PMID: 37701904; PMCID: PMC10493284.
5. Latif W, Lambrinos KJ, Patel P, Rodriguez R. Compare and Contrast the Glucagon-Like Peptide-1 Receptor Agonists (GLP1RAs). 2024 Feb 25. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. PMID: 34283517.