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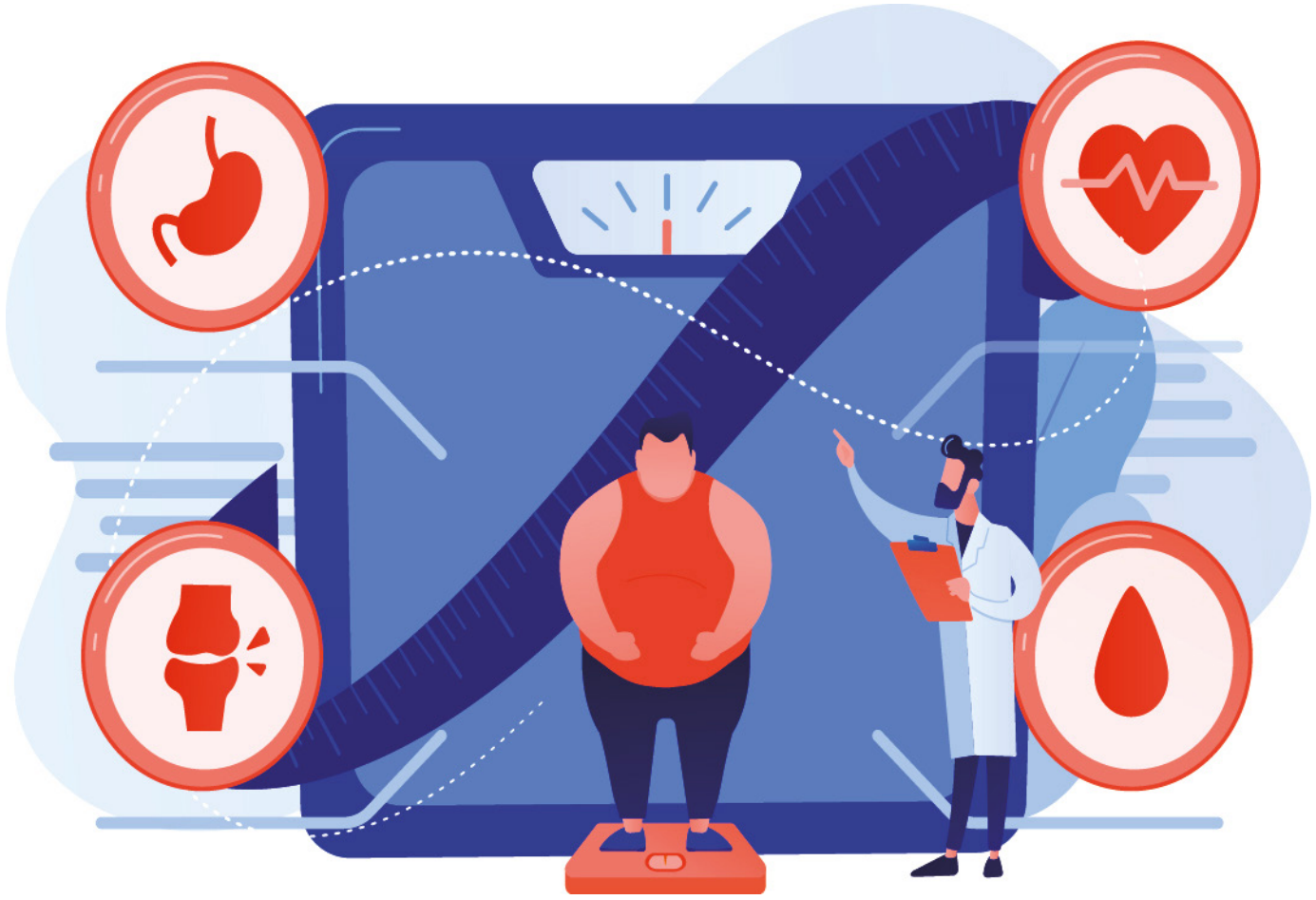

Diabetes and obesity, new approaches

The prevalence of obesity has increased worldwide, reaching epidemic figures in recent decades (1). This disease is associated with multiple comorbidities such as Type 2 Diabetes Mellitus, hypertension, dyslipidemia, and other cardiovascular diseases that cause a great impact on the individual's health and high social and health care spending. We have known for years the relationship between obesity and diabetes mellitus, so a holistic approach to these patients is necessary, including weight management to achieve good glycemic control. Hence the relevance that new therapeutic groups are acquiring, which allow simultaneous improvement of diabetes, obesity, and other cardiovascular risk factors.

Habitually, excess weight is classified based on the Body Mass Index (BMI), but it is also important to consider the presence or absence of comorbidities as a prognostic factor. In some people, overweight (BMI ≥ 25 kg/m²) and obesity (BMI ≥ 30 kg/ m²) have a significant negative impact at a psychological level, functional limitation in addition to other comorbidities, making it essential for early intervention.

The objective of this review is to recall the pharmacological treatments available to us for the joint management of diabetes and obesity.

TREATMENT

In overweight or obese patients, guidelines (2, 3) recommend weight loss of between 5-10% of body weight in 6 months, with the aim of achieving better glycemic control and a better management of cardiovascular risk factors. For this loss, we must initiate non-pharmacological treatment based on lifestyle changes, recommending a low-sugar Mediterranean diet and daily physical exercise. Similarly, we must review patients' treatments to modify those that may cause weight gain. If with this we do not achieve the weight or glycemic control goals, we must resort to the use of drugs that help reduce the body weight of our patient.

Below, we will discuss these drugs and their different characteristics.

- ***Selective inhibitors of the sodium-glucose cotransporter type 2 (SGLT2i)***

  Kidney plays an important role in serum glucose homeostasis through tubular glucose reabsorption carried out by these transporters, which filter around 180 grams of glucose per day.

  In healthy patients, the inhibition of this cotransporter is 30-50%, so of those 180g of filtered glucose, about 70-90g are lost in urine. This urinary loss is equivalent to 200 300 calories/ day, which contributes to the patient's weight loss. In addition to this weight decrease, it has been observed that blood pressure also decreases, the progression of chronic kidney disease is prevented in any stage, and hospitalizations due to heart failure decrease.

  They can be used in monotherapy (if intolerance/contraindication to metformin) or in combination with other oral antidiabetics or insulin. They present a very low risk of hypoglycemia. No dose adjustment is required in kidney disease, but their initiation is not recommended if eGFR is less than 30mL/min.

  Their main side effects are digestive discomfort, genitourinary infections, and volume depletion (discontinue in patients with gastroenteritis, decreased fluid intake, etc.).

- ***Glucagon-like peptide-1 receptor agonists (GLP-1 RA)***

  These drugs increase insulin secretion from pancreatic beta cells and glucose-mediated secretion, suppress glucagon secretion from alpha cells, and slow gastric emptying; these 3 factors are the main ones for significant reductions in glycemia since it is not degraded by DPP4 enzymes (which gives it a prolonged half-life). Similarly, they produce satiety, decreased appetite, and food intake, which causes body weight loss. They also help in the control of other cardiovascular factors, such as blood pressure control.

  Multiple drugs exist, both for oral and subcutaneous administration, with semaglutide being the most potent, with a weight loss of around 6 kg and a glycated hemoglobin reduction of approximately 1.6% (4). In terms of efficacy, dulaglutide and liraglutide follow (4).

  It is an option to consider in a patient with diabetes mellitus and overweight/ obesity. Although they cannot be used in monotherapy, they can be combined with other oral antidiabetics (except with DPP4 inhibitors) or insulin. They present a very low risk of hypoglycemia and can be used with chronic kidney disease except with eGFR < 15mL/min.

  These drugs are funded by the national health system in patients with poorly »

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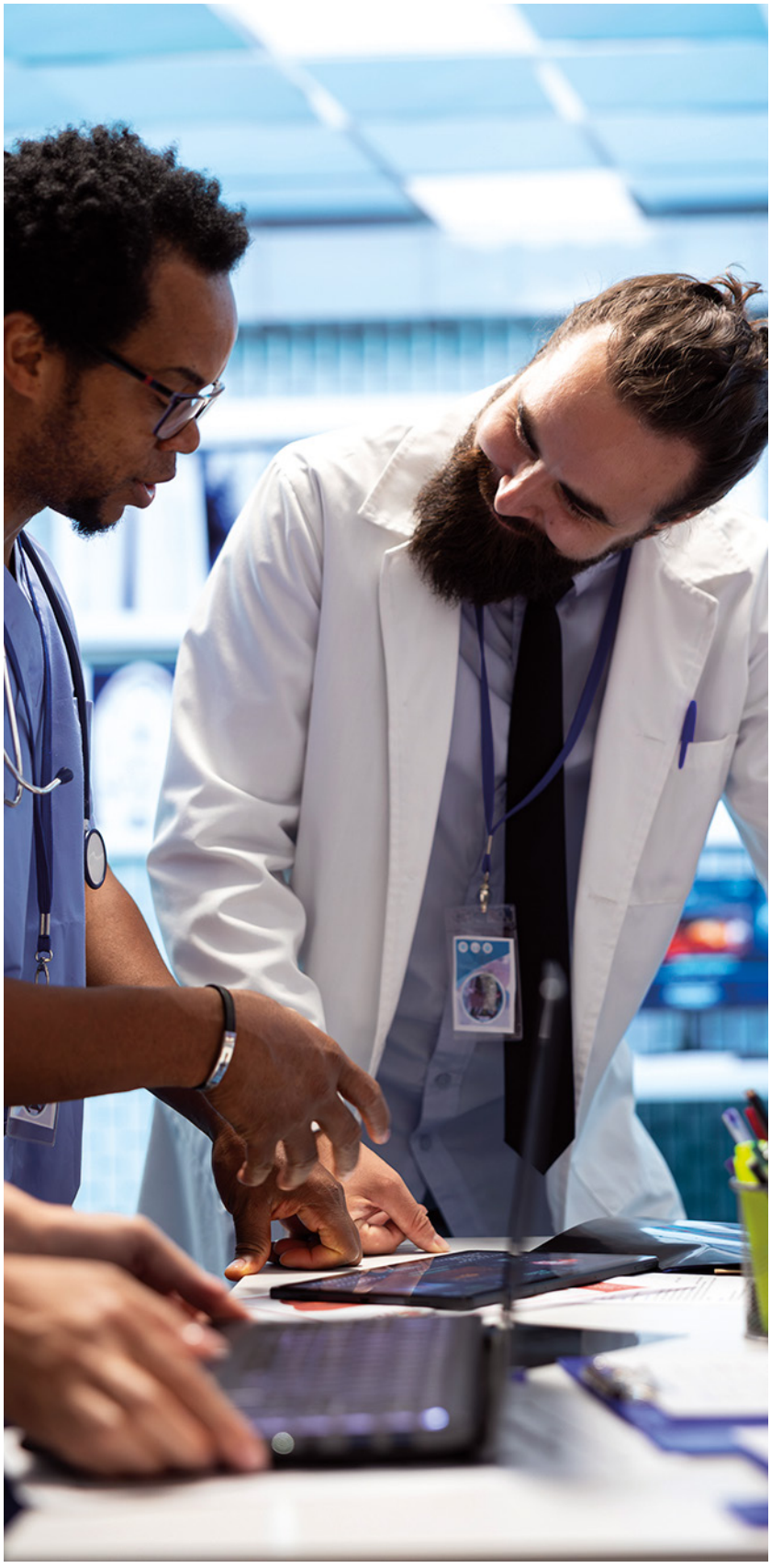

» controlled diabetes and a BMI ≥ 30 kg/m² with prior authorization and help reduce weight when accompanied by a hypocaloric and antidiabetic Mediterranean diet and physical exercise, especially strength training.

• Dual GLP-1/GIP agonist

Tirzepatide is the first dual agonist of glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide available on the market.

This drug improves the function of pancreatic beta cells and increases markers of insulin sensitivity (adiponectin, IGFBP1 and IGFBP-2), achieving a greater reduction in glucose levels, weight, as well as other cardiovascular risk factors. It causes a slowing of gastric emptying in addition to satiety, also acting at the level of the central nervous system.

The results of the SURPASS-2 study (3) conducted in obese patients with type 2 diabetes mellitus demonstrated the superiority of this drug in terms of glycated hemoglobin reduction (around 2% less) and body weight reduction (approximately 21% reduction = 10 kg less) vs other molecules.

Its administration is a weekly subcutaneous injection. No dose adjustment is required in chronic kidney disease, being a beneficial drug for slowing the progression of kidney failure due to its better glycemic control.

Its main side effects would be gastrointestinal (nausea, vomiting), being dose-dependent, so a gradual dose escalation of the drug is recommended to avoid these side effects. It has two absolute contraindications: medullary thyroid cancer and MEN type 2 neoplasms.

Currently, it is not funded by the national health system, but it is a very interesting and recommended option for all our patients with diabetes and overweight/obesity. Today, there are several lines of research on dual agonist drugs and even triple/quadruple agonists (5) that may modify the treatment of diabetes mellitus in patients with obesity in the near future. D

CONCLUSIONS

In these patients, it is fundamental to achieve body weight loss to improve their glycemic control and cardiovascular health. When choosing a pharmacological treatment for them, we must take into account the side and/or adverse effects of these drugs on the patient's weight, as well as review other treatments for different comorbidities that may cause an increase in it.

A new therapeutic approach for the treatment of diabetes is possible due to new pharmacological families, which act simultaneously on obesity and diabetes, achieving good results in both areas. For this reason, in this patient profile, we should take a more adipocentric than glucocentric approach.

Furthermore, it has been observed that achieving weight loss motivates the patient, which ultimately leads to greater adherence to pharmacological treatment.

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