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## Drug approach to treatment for obesity in adults: perspectives and considerations

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Obesity is considered a chronic disease and a serious public-health issue in Spain, as well as in many other countries, primarily because of it being a significant risk factor for multiple chronic conditions, including diabetes *mellitus* type 2, cardiovascular disease, respiratory disease, metabolic dysfunction-associated fatty liver disease (1), gastrointestinal conditions (gastroesophageal reflux, diverticulosis) (2,3), musculoskeletal difficulties, infertility, and even development of some malignancies such as postmenopausal breast cancer, and colorectal (4), endometrial, renal, esophageal (5), pancreatic (6), hepatic (7), and gallbladder neoplasms. Furthermore, weight loss, whether as therapy goal or voluntary, has been shown to be beneficial for virtually all these health conditions, the more so the greater weight loss (8).

When one bears in mind the obvious relationship between obesity and so many highly significant health conditions, obesity rates as found in Spanish adults and children/adolescents become even more alarming. One of the most recent surveys is that of the ENE-COVID (9), study, a nationally representative seroepidemiological survey of 57,131 subjects, where participants (77.0 % of contacted people) answered a questionnaire to collect self-reported weight and height, as well as multiple socioeconomic variables, which allowed an estimation of both crude and standardized prevalence rates for obesity and overweight in adults. In this study the gross prevalences of obesity and overweight were higher for males (obesity: 19.3 % versus 18.0 %; overweight: 63.7 % versus 48.4 %), whereas severe obesity (BMI > 40 kg/m<sup>2</sup>) was more prevalent in women (4.5 % versus 5.3 %). These prevalences increase with

age and disability, and decrease with education, census tract income, and municipality size. Differences by education level, relative census tract income, nationality or disability are clearly higher among women. Obesity by province oscillates between 13.3 % and 27.4 % in men and 11.4 % and 28.1 % in women, whereas excess weight ranges from 57.2 % to 76.0 % in men and from 38.9 % to 59.5 % in women. The highest prevalences are found in the southern half of the country and some northwestern provinces.

In summary, the prevalences of general obesity and abdominal obesity in Spain are high, but unevenly distributed among autonomous communities. Comparison with previous data shows a significant increase in weight overload, which points out the need for systematic monitoring and integral action (10). Furthermore, trends indicate that the prevalence of obesity has been on the rise in Spain and many other countries over the last decades. This may be due to dietary changes, sedentary lifestyles, and other environmental factors.

Since the prevalence of this condition increasingly involves millions of people around the world, the search for effective treatment strategies has become more intense. In this context, drug therapy has come to be a crucial component in the management of obesity, albeit with specific perspectives and key considerations. A defining characteristic of this approach is its ability to supplement lifestyle changes. While a balanced diet and regular exercise are key for weight control, drugs offer an additional tool in the fight against obesity. However, it is imperative to point out that medications should not be thought of as an independent solution; rather, they must be integrated into a holistic approach including dietary changes, physical activity, and psychological support.

Therapeutic interventions aimed at achieving significant weight loss (at least 10 % from baseline) have demonstrated their ability to induce remission in diabetes type 2 (DIRECT study) (11) and metabolic fatty liver disease (especially with dual agonists and triagonists), and to reduce the development of cardiovascular disease and even neoplasms (bariatric surgery). However, maintaining weight loss long-term remains a

challenge, especially in studies including dietary interventions. Therefore, drug-based approaches are increasingly considered, which seem to achieve significant, long-term sustained weight loss when using the newer molecules. Robust molecules in this regard (effectiveness and duration of effect) include semaglutide, a one-weekly subcutaneously administered GLP-1 receptor agonist (GLP1RA) that at 2.4 mg/week has been shown to achieve up to 15 % weight loss from baseline in obese individuals, with sustained effectiveness for up to 2 years (STEP 1 [12] and 5 [13] studies, respectively). Also, treatment discontinuation, which was analyzed in STEP 4, has shown the chronicity of the condition, and suggests the need for continued obesity therapy to maintain improvements in weight and health (14).

However, these magnificent results have now been surpassed by those of a dual GLP-1/GIP agonist, namely tirzepatide, which has achieved weight reductions of up to 20 % in people with obesity (SURMOUNT 1 study) (15), with an excellent response of metabolic fatty liver disease in a post-hoc study versus insulin degludec (SURPASS 3-MRI study) (16). These results were warmly welcomed by the general population, eager to have effective tools available in their fight against obesity.

Finally (for the time being), data have emerged on the effectiveness of retatrutide, a GLP-1/GIP/glucagon triagonist, with weight reductions of up to nearly 25 % and 100 % of responders, at least in terms of weight loss by 5 % or more (17).

These results show how powerful these molecules (and others under study, as CagriSema) are, with a very good safety profile and additional cardioprotective effects independent of their action on weight (SELECT study) (18).

All things considered, the latest studies of molecules acting on GLP-1, alone or in combination with GIP and glucagon, have demonstrated the high potency of these drugs in terms of weight reduction, persistent effect long-term, and cardiovascular protection in patients with obesity at high cardiovascular risk, with a fine safety profile.

However, at present in Spain, the most effective drug available for treating obesity is liraglutide 3 mg/day, a GLP-1 receptor agonist (GLP1RA) with indication for both adults and adolescents older than 12 years. Liraglutide 3 mg/day is indicated, in combination with low-calorie diet and increased exercise, for weight control in adult patients with a

baseline body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup> (obesity) or from  $\geq 27$  kg/m<sup>2</sup> to  $< 30$  kg/m<sup>2</sup> (overweight), presenting with at least one weight-related comorbidity such as impaired glycemia (prediabetes or diabetes *mellitus* type 2), hypertension, dyslipidemia, or obstructive sleep apnea. In adolescents older than 12 years liraglutide 3 mg/day may be used combined with healthy nutrition and increased physical activity, for weight control in the presence of obesity (BMI  $\geq 30$  kg/m<sup>2</sup> in adults according to international cutoffs) and body weight above 60 kg. This drug, however, lacks funding for patients with overweight/obesity and the aforementioned comorbidities, which often makes indication difficult. In contrast, indication and funding are available for a number of GLP1RAs in individuals with diabetes *mellitus* type 2 and concomitant obesity (BMI  $> 30$  kg/m<sup>2</sup>), including liraglutide, dulaglutide and semaglutide, which may be administered either subcutaneously or per os; notwithstanding this, it is well known that semaglutide 1 mg weekly is being used in people with obesity alone, despite its being a drug exclusively indicated for diabetes type 2. This circumstance, together with the “spontaneous” publicity provided by celebrities and influencers in social media, has resulted in rampant use of these drugs in settings often clearly outside medical indication, as well as in market shortages, the latter issue also probably due to difficulties in finding specific administration system components (injector pens). Despite the above, even if it sounds paradoxical, these drugs are underused in individuals clearly diagnosed with obesity, most likely because of absent financial coverage for obesity.

Therefore, the effectiveness of these newer molecules for weight loss and cardiovascular protection has been clearly demonstrated, hence we in the scientific community still wonder what does it take to start considering the coverage of these drugs, in the understanding that patients with a more favorable cost-benefit ratio will likely be considered first. As former president of the Spanish society for endocrinology and nutrition, and based on discussions held with a variety of colleagues, I dare say that scientific societies tending to persons with these health conditions would be delighted to cooperate with political representatives and financial policy makers to help solve this relevant public health issue.



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