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# Is semaglutide a target therapy for acquired hypothalamic obesity?

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The worldwide prevalence of overweight and obesity is approximately 39% and represents one of the major health concerns. Apart from the evidence that it increases the risk of several other costly diseases such as type 2 diabetes, cardiovascular disease, and cancer, two new pillars have attracted the attention of researchers and clinicians: (i) it is a chronic relapsing disease, (ii) the pathophysiology is strictly related to a disruption in regulatory neuroendocrine circuitry working in the brain, in particular at hypothalamic level [1, 2]. These pathways interact with the periphery, and regulate feeding and emotional behaviors, satiation and satiety, and energy expenditure [2–4]. In this complex scenario, hypothalamic obesity (HO) represents the fullback of these mechanisms and one of the most challenging phenotypes to manage efficaciously.

HO is characterized by abnormal and resistant to treatment weight (fat) gain due to structural injury to the hypothalamus or congenital hypothalamic dysfunction mainly due to genetic disorders [4, 5]. Hyperphagia is a hallmark of HO since leptin and insulin are unable to modulate feeding and energy signaling due to their disruption. Furthermore, peripheral leptin and insulin resistance complete the picture. Severe obesity, hyperphagia, psychological and self-esteem complications, decreased QoL, metabolic alterations, and high cardiovascular morbidity increase mortality and result in the need for a high multidisciplinary care [4, 6, 7].

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Genetic causes are characterized by a tremendous weight gain in the first years of life and are the best model to study the pathophysiology of HO, but fortunately, they are very rare [5]. On the other hand, CNS tumors are the commonest cause of acquired HO accounting for 25% of cancers in children < 15 years with an annual incidence of 35 cases/million/year. Among them, craniopharyngioma is the most frequent cause and has an overall incidence of 1.3–1.7 per million people/year, mainly children and young adults. Approximately 50–70% of patients with a diagnosis of craniopharyngioma develop HO [4, 8]. Furthermore, CNS tumors are frequently burdened by the presence of hypopituitarism due to damage of the hypothalamus and/or pituitary caused by the lesion or secondary to surgical or radiotherapy treatments [9].

To date, conventional lifestyle interventions failed in most of the patients. Bariatric surgery is quite ineffective on long-term with a rebound effect since peripheral neuroendocrine and microbiota changes are less pronounced, hyperphagia and its brain signature at functional MRI do not disappear [10], suggesting that the integrity of the hypothalamus has a crucial role also for surgery procedures. Moreover, safety and the risk of nutrient and drug malabsorption should be strictly considered in these fragile patients. As a consequence, several drug treatments with a central action on the hypothalamus or other areas involved in feeding or hedonic behaviors or acting on hyperinsulinemia and insulin resistance have been proposed for the management of HO in the last 20 years. Truncal vagotomy, octreotide, diazoxide and metformin, sibutramine, fluoxetine and fenfluramine, dextroamphetamine, sibutramine, caffeine with ephedrine, and oxytocin are some of the investigated treatment strategies, but no one of them was satisfying in inducing weight-loss or decreasing hyperphagia. Furthermore, quite all of them were burdened by a plethora of clinically unsustainable adverse events [4, 7]. A recent phase 2 trial with Tesomet (tesofensine combined with metoprolol) demonstrated in 21

patients with acquired HO a mean weight loss of 6.3% after 6 months of treatment with acceptable and manageable side effects (headache, dry mouth, and sleep disturbances) [8].

More recently, setmelanotide, a MC4R agonist, has been patented to act on the leptin-melanocortin pathway upstream of the genetic defect that disrupt this signaling. The molecule was effective in promoting sustained weight loss and decreased hyperphagia in patients older than 6 years affected by some genetic obesity disorders (POMC and LEPR deficiency, and Bardet-Biedl syndrome) [11]. A phase 2 trial in other causes of HO has recently been published demonstrating a decrease in weight or BMI from 5 to 26% at 12 months [12], and in some countries like Italy it is granted for from 6 years of age to the end of adolescence in patients with severe HO secondary to craniopharyngioma coupled with comorbidities [13]. However, this drug remains currently only available for a small fraction of patients with HO and is burdened by high costs. Furthermore, its long-term safety and effects on cardiovascular risk have not been proven yet.

In the accompanying papers to this commentary, both Svendstrup [14] and Gjersdal [15] and coworkers demonstrate that semaglutide is efficacious in treating acquired HO in patients with CNS tumors involving the hypothalamus. A total of 30 patients in the two studies, 19 out of them with a history of craniopharyngioma, were treated with semaglutide for 6 [15] or 24 months [14]. Quite all of them experienced massive increasing body weight after the disease diagnosis. Twenty-one patients were naïve to any drug for the treatment of obesity, and 9 patients of the cohort of Svendrup et al. were switched to semaglutide from daily liraglutide. After the up-titration phase, the median tolerated dose of semaglutide at the end of the period in both studies was ∼1.7 mg/weekly. All, but one patient, lost weight during the studies. In the mixed cohort of Svendrup and coworkers, the maximum achieved weight loss was 26% of the baseline body weight at 12 months, and 15 and 2 patients lost more than 10% and 20% of initial body weight, respectively. No differences between pretreated and naïve patients to Glucagon-like peptide-1 receptor agonists (GLP1-RA) were observed, neither about the presence of diabetes nor pituitary hormonal substitution [14]. In the 4 craniopharyngioma cases of Gjersdal and coworkers weight reduction was 11.3–22.4 Kg from initial body weight, suggesting a reproducible effect among cohorts. Furthermore, body composition was analyzed, and authors reported a similar decrease in body fat and lean mass, without affecting bone mass. Uncontrolled eating (UE) and emotional eating (EE) diminished significantly in these 4 patients [15].

All these findings are encouraging for the management of HO. GLP1-RAs are drugs efficacious and well tolerated in almost all the patients managed with tailored titration dose strategies. Furthermore, GLP1-RAs resulted in a decrease in UE and EE in several studies on obesity [16–18]. These effects are explained by experiments in animal models that showed that the intracerebroventricular infusion of GLP-1 is followed by a reduction in food intake coupled with weight loss, by modulating the orexigenic (NPY/AgRP) and anorexigenic (POMC/CART) feedback loops during fasting [4, 7, 19]. Furthermore, these molecules affect also the central pathways implicated in rewards and energy expenditure [20].

Of note, semaglutide reduced cardiovascular mortality by 24% in obesity, also without diabetes [21], and lowered the risk of 10 obesity-related cancers compared with insulin or metformin in patients with diabetes [22]. The pleiotropic effects on total morbidity and mortality identify GLP1-Ras, in particular semaglutide, as good candidates for the global management of HO, apart from weight loss, due to the multifaceted mechanism of action, beyond the hypothalamic regions.

Before the two studies object to this commentary, several case reports or recent small randomized control trials with other GLP1-RAs (liraglutide/exenatide) were published [23–26], reporting a mean weight loss from negligible to 13 Kg or BMI loss of 1–4%. These results are inferior to what was achieved in the studies of Svendstrup [14] and Gjersdal and coworkers [15] with semaglutide that reached a median weight loss of 26%. The weight loss obtained in previous papers with liraglutide/exenatide is in line with weight loss also reported in a recent study on genetic HO [27, 28], meanwhile that with semaglutide with the first case report in an adolescent patient with a history of HO due to craniopharyngioma who achieved a weight loss of 30 Kg (-24% respect to the baseline) [29]. The differences in efficacy among molecules of the same class could be advocated by the fact that semaglutide differs from other GLP-1RAs on the market for a longer half-life and a generally more potent effect on weight loss [16–18]. If compared with liraglutide, the most similar molecule at the chemical level, it activates different areas of the CNS, such as the parabrachial nucleus, and different GLP1-R subpopulations and it is suggested to cross the blood-brain barrier more effectively [3, 16–18, 20]. The action on other circuitries implicated in reward regulation is in line with the reduction of UE and EE observed in the study of Gjersdal et al. [15] as well as in the first case report [29]. Furthermore, the effect on central modulation of energy expenditure could be one of the mechanisms through which semaglutide is more effective in reducing weight loss in HO compared to other GLP1-RAs. Moreover, as previously introduced, high insulin levels are a feature of HO due to the lack of feedback on the vagus nerve, indeed semaglutide's action on insulin secretion amount and shape, coupled with a decreased insulin resistance, could be other two master regulators of the

achieved weight-loss. Unfortunately, no one of the studies investigated these aspects, differently from Sciacovelli and coworkers [29], but HbA1c improved [15].

Since in both studies [14, 15] a weight loss > 10% has been achieved, we could hypothesize that most of the adiposity-based chronic diseases were improved, delayed, or prevented [3], although this aspect has not been deeply investigated by the Authors also because to the short follow-up time.

So what is the impact of these two studies on acquired HO? Surely, the authors are likely to provide insights into the management of factors that contribute to HO pathogenesis. Semaglutide treatment does not come as a total surprise given that it is going to represent one of the cornerstone treatments for obesity, in particular when associated diseases are present. However, previously unsatisfying results with exenatide and liraglutide in HO could have hampered the propensity to further try semaglutide in this obesity phenotype. In this scenario, the papers by Svendstrup et al. [14] and Gjersdal et al. [15] open exciting perspectives to design tailored randomized control trials on the efficacy of semaglutide in HO. However, in this view, further mechanisms and features of patients should be deeply investigated; outcomes apart from weight loss should be included to understand where is the place for semaglutide in the clinical management flow-chart.

First, lifestyle strategies have not been proposed in these two studies, likely due to previous failures or low adherence. However, structured intensive behavioral, nutritional, and physical activity therapy could synergize with the drug, as demonstrated in simple obesity [1, 3, 5]. Gjersdal et al. reported a decrease in muscle mass at dual-energy x-ray absorptiometry [15]. Information regarding the amount of weight loss also due to muscle mass is still anecdotal in the literature concerning the number of people treated in both pivotal randomized control trials, as STEP and SELECT trials [21, 30, 31], and spontaneous studies [32]. A recent review reported a lean mass loss from almost 0–40% of total weight reduction [32]. The SURMOUNT-1 trial on tirzepatide, a glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonists, has demonstrated a percent reduction in fat mass approximately three times greater than the reduction in lean mass; however, the loss of fat-mass ratio respect to lean-mass was similar to that reported with lifestyle-based and surgical treatments for obesity [1, 32]. Indeed, data on muscle loss are warranted in HO patients in whom low resting energy expenditure has been reported [33]. Parallel strategies to preserve skeletal muscle could be of primary importance.

Second, hypothalamic damage in the posterior hypothalamus and mammillary body has been associated with an increased risk of HO. Unexpectedly, the extension of hypothalamic injury at MRI, mainly in the mammillary body, has been associated with a greater response to weight loss in patients with HO treated with exenatide. One hypothesis is that damage in the hypothalamus promotes higher positive feedback on extra-hypothalamic sites of action to GLP1-RAs, where pathways remain intact in HO patients, including hindbrain and mesolimbic reward areas, and hippocampus [24]. Indeed, MRI findings could help identify patients more responsive regarding weight loss and, maybe, hyperphagia, considering that semaglutide crosses more the blood-brain barrier. In parallel, the timing of weight increase (before or after surgery/radiotherapy treatments) constitutes another potential marker of response to the treatment.

Third, since the hypothalamus has been destroyed, different long-term feedbacks concerning common obesity could be observed. Studies on the maintenance of the anti-obesity effect and timing of plateau are needed, coupled with findings on the prevention of cardiovascular-related diseases.

Indeed, the studies of Svendstrup et al. [14] and Gjersdal et al. [15] give us important clinical insights into the potential use of semaglutide as a pharmacological treatment for acquired HO. Confirmatory studies with further pleiotropic outcomes are needed to validate these findings and help in selecting patients. Drug-safety considerations are mandatory in the future also in this context, and national and international trials are welcome. So, clinicians and researchers are you ready to use and study more semaglutide in acquired HO?

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## Declarations

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