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Review

The complex relationship between obesity and the somatropic axis: The long and winding road

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ABSTRACT

Despite the considerable body of evidence pointing to a possible relationship between the state of the adipose tissue depots and regulation of the somatotropic axis, to date the relationship between obesity and low growth hormone (GH) status remains incompletely understood. The low GH status in obesity is mainly considered as a functional condition, largely reversible after a sustained weight loss. Moreover, due to the effects of the adiposity on the regulation of the somatotropic axis, the application of GH stimulation tests in obesity may also lead to an incorrect diagnosis of GH deficieny (GHD). On the other hand, similar to patients with GHD unrelated to obesity, the reduced GH response to stimulation testing in obese individuals is associated with increased prevalence of cardiovascular risk factors and detrimental alterations of body composition, which contribute to worsening their cardio-metabolic risk profile. In addition, the reduced GH secretion may result in reduced serum insulin-like growth factor (IGF)-1 levels, and the concordance of low peak GH and low IGF-1 identifies a subset of obese individuals with high cardiovascular risk. Furthermore, after weight loss, the normalization of the GH response and IGF-1 levels may or may not occur, and in patients undergoing bariatric surgery the persistence of a low GH status may affect the post-operative outcomes. In this review, we will provide an overview on some clinically relevant aspects of the relationship between obesity axis and the somatotropic axis in the light of the recently published research.

1. Introduction

Growth hormone (GH) and insulin-like growth factor (IGF)-1 are the main regulators of linear growth [1]. However, the lifelong involvement of the somatotropic axis in the regulation of metabolism and body composition as part of the overall regulation of body weight across the feeding/fasting cycle has become increasingly evident [2]. GH and IGF-1 play an important role in the maintenance of normal body composition, by exerting both anabolic and catabolic actions on different tissues in the human body, with overall stimulatory effects on protein synthesis in muscle and lipolysis in adipose tissue [3]. Our understanding of the complex relationship between obesity and the somatotropic axis started to be unraveled in the 1960s from the observations that obesity induced by lesions of the ventromedial hypothalamic nucleus was associated to GH suppression and reduced linear growth in animals [4]. Since then, a growing body of evidence has accrued supporting the hypothesis that the state of the adipose tissue depots and the regulation of the somatotropic axis are closely related [5–9].

In spite of the considerable effort expended in producing clinical and experimental data regarding the possible involvement of the low GH status in amplifying the cardio-metabolic risk profile in obese individuals, the relationship between obesity and the somatotropic axis remains incompletely understood. In this respect, the question arises of whether the impairment of spontaneous and stimulated GH secretion that characterizes obesity induces a true GH deficiency (GHD) according to the current guidelines [10], or represents only an epiphenomenon of obesity, evoking the proverbial chicken and egg question. In fact, although generally reversible after sustained weight loss, the low GH status in obese individuals is associated with increased prevalence of cardiovascular risk factors and detrimental alterations of body composition which contribute to worsening their cardio-metabolic risk profile. This review was aimed at pinpointing some of the key aspects of the relationship between obesity axis and GH/IGF-1 in light of recently published research.

2. The first steps along the road: brief highlights on the GH/IGF-1 axis

The GH/IGF-1 axis is a finely tuned endocrine system with multiple levels of control including neuroendocrine mediators, tissue and soluble receptors, and carrier proteins [11]. The major physiologic and bioactive component of GH is a 22 kDa single-chain of 191 amino acids; its

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pulsatile secretion from the anterior pituitary is centrally controlled by GH-releasing hormone (GHRH), somatostatin (SS) and GH-releasing peptides, although a range of peripheral signals contribute to the regulation. GH acts through a single transmembrane receptor (GHR) that is structurally related to PRL and cytokine receptors. In humans, the GHR is highly expressed in many peripheral tissues and the liver, where GH stimulates the synthesis of IGF-1. In turn, IGF-1, the key transcriptional target of GH signaling, influences GH secretion through a classic negative feedback system. In addition to IGF-1, a number of peripheral factors have long been recognized as key regulators of GH secretion, along with nutritional status, glucose and fat metabolism, primarily free fatty acids (FFA), and circulating hormones, such as insulin, ghrelin, adiponectin, and leptin. In particular, clinical and experimental studies show an inhibitory role of insulin on GH release and mRNA expression of GHR [3]. IGF-1 is a single, nonglycosylated, 7.6 kDa protein integrated in the IGF regulatory system [12]. This system consists of two ligands (IGF-1 and IGF-2), two cell-surface receptors (type I and type II IGF receptors) and six regulatory binding proteins (IGFBP-1-6], associated with IGFBP degrading proteases. Free IGF-1, which accounts for less than 1% of the total circulating IGF-1, is responsible for the bioactivity on target tissues. IGF-1 circulates within the intravascular space as part of a ternary complex with ALS and IGFBP-3, the predominant plasma binding globulin regulated by GH concentration, constituting both a reservoir and a carrier system for IGF-1. However, IGFBP-1 and IGFBP-2 are also important determinants of IGF-1 bioactivity, where IGFBP-1 and IGFBP-2 are active regulators of IGF-1 effects and bioavailability, respectively. Aside from GH, many different factors have been reported to affect IGF-1 metabolism, such as age, gender, body composition, nutritional driven components, and glucose homeostasis [13]. Insulin is involved in regulating the IGF system mainly through modulating the IGFBPs, which in turn regulate insulin sensitivity *via* bioactive IGF-1, with a central role for IGFBP-2; both glucose and insulin down-regulate the secretion of IGFBP-1 by the liver, while insulin *per se* regulates IGFBP-2 [14].

GH activates multiple intracellular signal transduction pathways, leading to the transcription of several genes, including the components of GH/IGF-1 axis, such as IGF-1, IGFBP3, and ALS [3,15]. GH receptor (GHR), Janus kinase (JAK)2, and signal transducer and activator of transcription (STAT) proteins are mainly involved in GH signaling cascade. Following the GH binding to GHR, a member of the class I cytokine receptor superfamily, the tyrosine kinase JAK2 is activated. Upon recruitment to the GHR–JAK2 complex, the STAT proteins are phosphorylated, with STAT5b as the principal transcriptional effector. Two other GH signal transduction pathways are the RAS/MAPK and the phosphatidylinositol 3′-kinase (PI3K)/Akt pathways. Aside from the internalization of GHR, GH/IGF1 signaling is also modulated by the suppressors of cytokine signaling (SOCS) 1–3, a family of intracellular proteins with a key role in regulating cytokine-activated JAK2/STAT pathways, resulting in a complete block of GHR-mediated signaling [3,16]. GH directly affects adipocyte metabolism by inhibiting the lipoprotein lipase; furthermore, GH increases the hormone-sensitive lipase activity by the activation of the β-adrenergic receptor. Through these effects, GH stimulates the preferential oxidation of lipids, directing the energy from metabolic processes towards the synthesis of proteins. Moreover, GH down-regulates the expression of 11β-hydroxysteroid dehydrogenase type 1, the enzyme that amplifies the action of glucocorticoid in visceral adipose tissue by stimulating the conversion of inactive dehydrocorticosterone to active corticosterone [3]. GH also modulates the expression of lipid droplet proteins, such as CIDE-A (cell-death-inducing DFF45-like effector), and the secretion of adiponectin, thus promoting a more favorable peripheral adipose tissue distribution [3]. More recently, the evidence that GH differentially regulates the NF-kB activity in adipocytes and macrophages suggests a modulating role for GH on chronic inflammation involved in obesity-associated insulin resistance [17]. IGF-1 also has metabolic actions on its own in regulating lipolysis, proteolysis and insulin resistance as part of the IGF-1/insulin system. Other effects, such as the stimulation of preadipocyte proliferation, differentiation, and survival, are produced by the up-regulation of IGF-1 secretion. Above all, a "fine tuning" of IGF-1 signaling cascade, especially the IRS-1/PI3K/Akt pathway, is critical for proper adipogenesis [18]. In obese individuals this integrated regulatory system is disrupted at multiple points and a number of central and peripheral regulative factors might contribute to affecting their GH status [9].

3. Clinical and experimental evidence linking obesity and low GH status

Obese individuals with low GH status exhibit detrimental changes in the cardiovascular risk profile and body composition [19,20] closely resembling those observed in patients with GHD syndrome and Prader–Willi syndrome (PWS). Adult GHD syndrome is a well-recognized acquired clinical entity commonly due to hypothalamic pituitary disorders and/or their treatments, such as surgery and radiotherapy [21]. GHD patients commonly present with a metabolic syndrome characterized by unfavorable plasma lipid profile [22], increased cardiovascular morbidity and detrimental changes in their body composition due to increased fat mass and reduced muscle mass [10]. The increase in body fat, mainly the intra-abdominal fat, associated with decreased bone mineral density, muscle strength, exercise capacity and cognitive function, has led to the therapeutic use of GH replacement in adults with severe GHD [23]. Interestingly, GH replacement therapy improves the metabolic alterations and reduces the visceral adipose tissue, although with minimal changes in total body weight. PWS is the most common known genetic cause of marked severe obesity characterized by hyperphagia, muscle hypotonia, short stature, mental retardation, and multiple endocrine dysfunctions, including hypogonadism and reduced GH secretory capacity. PWS patients presented with an extreme increase in body fat mass that is more marked than that observed in obese subjects with comparable BMI [24]. Albeit the beneficial effects of GH treatment on growth and body composition have been clearly demonstrated in children with PWS, epidemiological studies have pointed out the occurrence of sudden death during initiation of GH mainly related to severe obesity and sleep-disordered breathing, leading to a call for cessation of its use [25]. In addition, experimental animal models of altered signal-transduction involved in the cellular responses to GH have been produced to investigate the role of reduced GH signaling in adiposity [26,27], such as the STAT5b knockout mouse, the GH receptor gene disrupted, knockout, or null mouse ($GHR^{-/-}$), containing a disruption in the GH receptor/GH binding protein gene which completely disrupts GH signaling, or the GH receptor antagonist transgenic mice expressing a GH analog which decreases GH signaling by competing with GH for binding to the GHR. All of these models are variably characterized by dwarfism, low plasma IGF-1 concentrations and obesity.

4. Low GH status in obese individuals: the crossroad of the road

Changes in the cardiovascular risk profile and body composition in obese individuals with low GH status are associated with increased cardio-metabolic sequelae [28–30], which are significantly worse compared to those found in obese individuals without impairments in the somatotropic axis [31,32]. Therefore, the focus has shifted to the possible contribution of the low GH status in amplifying the cardio-metabolic risk profile in obese individuals, likewise to GHD patients.

Major criticism considering obese individuals with low GH status as GHD patients is that this is a functional status and that it might reverse with weight loss. According to this view, the low GH status in obesity represents an acquired "functional" defect, rather than a pre-existing disorder. This issue harbors the questions of whether the presence of the low GH status has a clinical relevance in obesity and if weight loss does really normalize GH status. Although the exact mechanisms responsible for the altered GH secretion in obesity still need to be clarified, the vast majority of clinical data indicates that regardless of a normal pituitary function the endogenous GH secretion is markedly reduced

compared to age-matched controls in visceral obese individuals [5]. In particular, the reduction in the half-life of GH is associated with reduction in both frequency and amplitude of GH secretory bursts and increase in GH metabolic clearance rate, with the net result of low plasma GH levels [9]. Additionally, the GH response to a number of pharmacological challenges such as the insulin tolerance test (ITT) or GHRH + arginine, is definitely blunted [31,33]. The neuroendocrine alterations underlying the low plasma GH levels in obesity include dysregulation of GHRH, SS, and ghrelin pathways, although a key role is also played by perturbations in obesity-related metabolic factors, such as hyperinsulinemia and excess of circulating FFA. The hyperinsulinemia associated with insulin resistance in obesity has been reported in contributing to a reduced GH secretion [3], likely by increasing the hypothalamic somatostatin release. As commonly seen in obese individuals, the inhibitory role of high circulating FFA is supported by the restoration of GH release after the administration of the antilipolytic agent acipimox [34]. This evidence indicates that high circulating FFA might be responsible for a low GH status *via* the derangement of a classical endocrine feedback loop between GH and FFA released by GH-induced lipolysis. Similarly, Orlistat, a gastrointestinal lipase-inhibitor, is effective in inducing a weight-independent increase in peak stimulated GH, IGF-1 levels, and IGF-1/IGFBP-3 ratio along with reduction in post-prandial FFA [35]. The acute reduction in circulating FFA induced by acipimox significantly increases the stimulated GH secretion only in obese individuals without organic GHD [36]. Regardless of FFA, a chronic state of leptin or insulin excess, as well as overeating *per se* or deficient ghrelin secretion, probably contributes to the impaired GH secretion. In addition, the severity of the defect in GH secretion is proportional to the degree of obesity, and an increase in each unit of body mass index (BMI) reduces the daily secretion of GH by 6% [37]. Currently, the central point is whether the reduced GH secretion in obesity might also result in reduced serum IGF-1 levels, thus configuring a true clinical condition of GHD. This is particularly relevant considering the close link between low IGF-1 levels and the pathogenesis of type 2 diabetes, metabolic syndrome, cardiovascular disease, and chronic inflammation [38,39]. In fact, a number of clinical studies showed that unlike patients with GHD unrelated to obesity, where total and free IGF-1 levels are mainly lower than in healthy controls [8], in obese individuals total IGF-1 may not be reduced to the degree predicted by GH levels; furthermore, other studies have reported relatively increased amounts of free IGF-1 which could be responsible for an enhanced feedback inhibition of GH release [40]. With particular regard to free IGF-1 determinations, these conflicting results could reflect methodological differences throughout the studies. Nevertheless, the heterogeneity in IGF-1 levels might partly be due to the effects on the IGF regulatory system of different factors associated with obesity, such as adipose tissue distribution, glucose homeostasis, hyperinsulinemia, and FFA. More importantly, the hyperinsulinemia associated with insulin resistance in obesity may variably influence free IGF-1 levels, linked to a concomitant reduction in IGFBP-1 and IGFBP-2 levels and high IGFBP proteolysis activity, which in turn are responsible for the negative feedback on somatotropic cells [41]. Both IGF-1/IGFBP-3 molar ratio, a rough estimate of free IGF-1, and ultrafiltrated free IGF-1 have been found to be significantly decreased in obesity; however, visceral adipose tissue, rather than adiposity *per se*, has been reported to correlate inversely with circulating total IGF-1 levels [8,42]. Anyway, the biological activity of IGF-1 measured as bioactive IGF-1, a method which incorporates the complex interactions between IGF-1, IGF-2, IGFBPs, proteases, and the IGF-1 receptor, might not be reduced in obese individuals [41]. In obesity this finding suggested that the enhanced sensitivity to GH at the level of the liver could maintain a normal IGF-1 activity despite the severely reduced endogenous GH secretion. Low IGF-1/IGFBP-3 molar ratio and low IGF-1 levels were found in individuals with hepatic steatosis, as a marker of a common pathway linking hepatic steatosis and low IGF-1 to metabolic syndrome and atherosclerosis [43]. Accordingly, we reported a significant negative correlation between components of the IGF-1 axis and the severity hepatic steatosis in overweight/obese subjects [44]. In this complex scenario, the strongest evidence is the link between increased visceral adiposity and low somatotropic axis. A number of factors arising from excess ectopic fat storage (e.g. visceral, epicardial or liver fat), including pro-inflammatory mediators, can independently affect the secretory mechanisms of GH and IGF-1 and reduce IGF-1 bioactivity [45]. Therefore, it is possible that the combination of multiple perturbations along the somatotropic axis might be responsible for different degrees of impairments of GH and IGF-1 secretion in obese individuals. The hypothetical maladaptive mechanisms likely involved in the network operating between obesity and the somatotropic axis are shown in Fig. 1. The concordance of low GH and low IGF-1 could have pathophysiologic relevance in increasing the accrual of adipose tissue and contributing to long-term metabolic and cardiovascular complications in obese individuals. In this respect, a recent report by Stanley [46] has demonstrated that low IGF-1 circulating levels and low peak stimulated GH in obesity were not always associated in the same obese individuals of both genders; however, if this were the case, then this association identified a subset of obese individuals with an increased cardiovascular risk. In particular, obese individuals with reduction of either IGF-1 or peak stimulated GH presented higher carotid intima-media thickness compared to an obese peer with normal IGF-1 and peak stimulated GH. In line with these data, we have also previously reported a discordance between peak stimulated GH and IGF-1 in obese females who were candidates for bariatric surgery [47], although in our series the discordance rate is far lower than in those reported by Stanley [46] (8.3% vs 31.6%). However, phenotypic characteristics of the subjects studied, for example degree of obesity, age and gender, may have accounted for the different discordance rates between the two series. These findings provide evidence that obese individuals could be present with an effective, though functional and reversible, low GH status. This condition might serve as a vicious circle that is reinforced with further accumulation of ectopic adipose tissue and increase in cardio-metabolic risk factors. In contrast, Pijl [48] found that, by using the deconvolution analysis of 24-h plasma GH concentration profiles, the GH neurosecretion remained altered after weight loss in premenopausal women with large visceral fat area, suggesting a primary role for hyposomatotropism in favoring the preferentially store excess fat in visceral adipose tissue in these women. In this regard, variable degrees of impairment of the somatotropic axis may be part of the maladaptive endocrine-metabolic changes likely responsible for the phenotypic variability among equally obese subjects [8,49].

The restoration of GH status along with weight loss, the long-lasting maintenance of weight loss in obese patients after bariatric surgery offers an interesting opportunity to evaluate this statement. Stimulated GH secretion significantly increases after biliopancreatic diversion (BPD) [50]. Partial recovery of GH secretion is also observed after Roux-en-Y gastric bypass (RYGB) [51]. On the other hand, although with some discrepancy [52,53], post-operative IGF-1 secretion shows a long-lasting impairment, similarly to that evidenced after nonsurgical weight loss, presumably linked to the catabolic state induced by BPD [54] and RYGB [55]. In the same series of obese female candidates for bariatric surgery reported above [47], we found that after laparoscopic adjustable gastric banding about a third of the patients with baseline low GH status restored their peak GH response: However, another fifth had IGF-1 levels still below the normal range calculated according to age normative ranges [10], with a post-operative discordance rate that was more than double the pre-operative value (8.3% vs 19.4%). Hence, likewise to weight loss after a long-term calorie restriction [8], the increase in IGF-1 levels along with the restoration of GH response to stimulation testing may or may not occur after bariatric surgery. In this context, the dissociation between GH and IGF-1 might be a marker of a subtle and persistent catabolic state probably due to bariatric procedures. Interestingly, excess of weight loss and fat mass loss were higher in patients who normalized their GH/IGF-1 axis after surgery than in those who did not [47]. We verified the influence of persistent failures

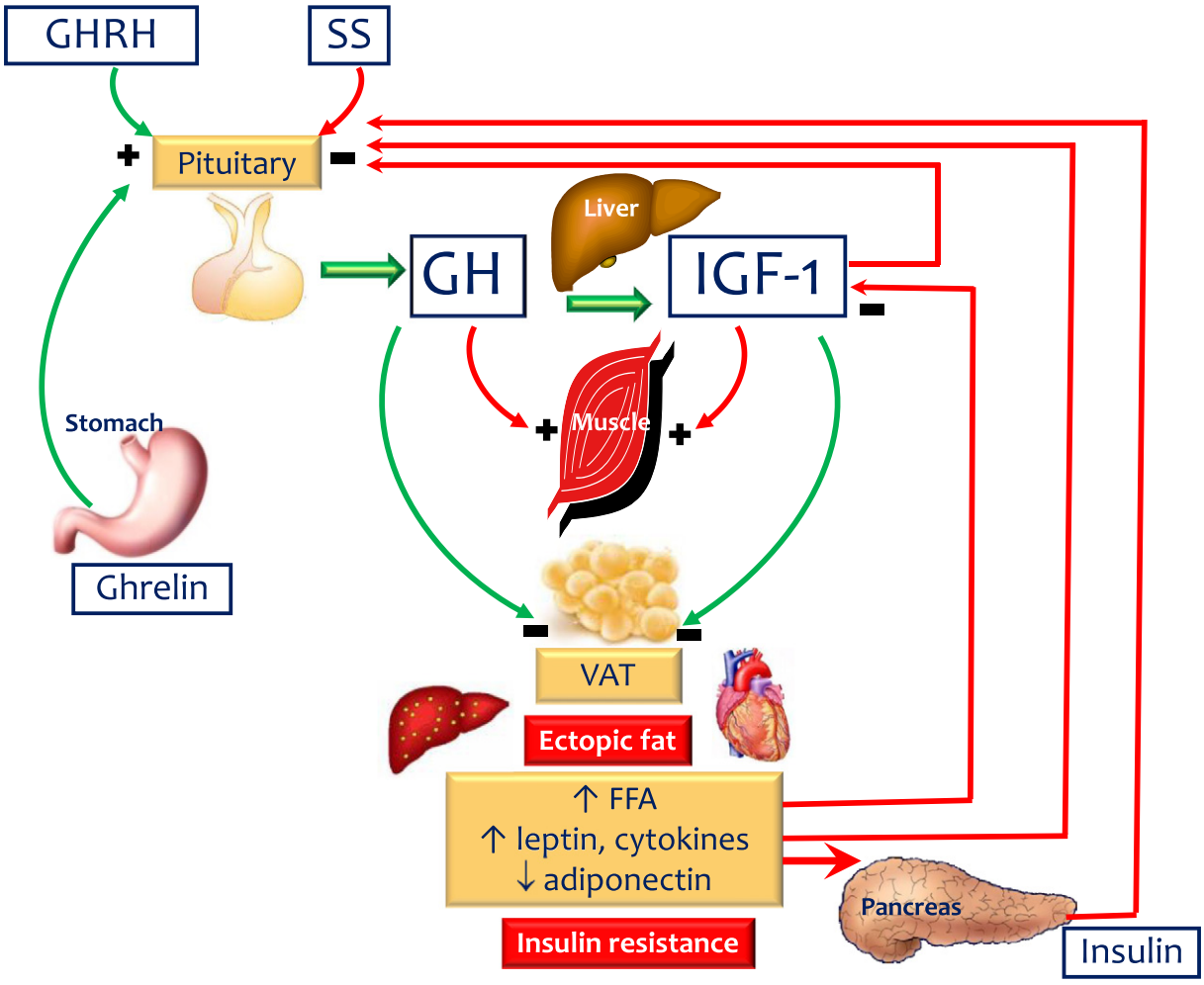

Fig. 1. The hypothetical maladaptive mechanisms likely involved in the etiopathogenesis of obesity-related alterations in GH/IGF-1 axis. The elevation of circulating FFA, adipokines and cytokines induced by increased visceral adipose tissue or other ectopic fat depots, such as hepatic steatosis or epicardial fat, is responsible for insulin resistance and is also able to markedly affect the normal feed-back control system operating in the GH/IGF-1 axis. The "functional" low GH/IGF-1 axis, on turn, might act on body composition by inducing unfavorable changes in body composition similarly to those observed in GHD, therefore contributing to worsen the insulin resistance state and the associated metabolic sequele. SS, *somatostatin*; GHRH, *growth hormone-releasing hormone*; GH, *growth hormone*; IGF-1, *insulin-like growth factor-1*; FFA, *free fatty acids*.

of the GH/IGF-1 axis on the weight loss outcomes of bariatric surgery in a larger series of obese subjects of both genders, allowing us to suggest the investigation of GH/IGF-1 axis in the pre-operative evaluation of obese candidates for bariatric surgery [49].

5. Further steps along the road: how to diagnose low GH status in obesity

Body fat, metabolic and nutritional status are the main confounding factors in the interpretation of biochemical tests commonly used in the diagnosis of GHD [10]. Adiposity might account for about 20% of the variability in peak GH response after provocative tests in both children [56] and in adults; it has been calculated that the GH response after GHRH + arginine testing was reduced 1.02 μg/L for each 1 cm increase in waist circumference, independent of BMI [33], and waist circumference represents the main predictor of low peak GH [57]. Considering the pulsatile nature of GH secretion, a correct diagnosis would require multiple sampling to obtain a 24-hour integrated GH profile. Conversely, serum IGF-1 and IGFBP-3 levels show only minor fluctuations and represent a stable and integrated measurement of GH production and its peripheral effects. Nevertheless, although IGF-1 levels <2 standard deviation below the age-matched mean is strong evidence for significant GHD, a provocative test of GH reserve is required for many adult patients with suspected GHD. The assessment of the GH secretion is commonly performed using pharmacological challenges such as ITT or GHRH + arginine. The latter one, using the effect of arginine in potentiating the response to GHRH *via* inhibition of the hypothalamic release of somatostatin, is currently considered the favorite diagnostic tool due to its high specificity and sensitivity, as well as tolerability [36]. GHRH + arginine is also the only test for which BMI-dependent variability of GH responsiveness has been investigated [58], with the definition of 4.2 μg/L as the appropriate GH cut-off in adults with BMI > 30 kg/m^2 [59]. Using this new cutoff value of the GHRH + arginine test, about 1/3 morbidly obese individuals presented a low peak stimulated GH [31]. Very recently a 1-μg/L peak GH cutoff level for the diagnosis of adult GHD in overweight/obese individuals using the glucagon stimulation test has been provided [60].

Important criticism to the application of GH stimulation tests in obesity is that it might lead to an uncorrect diagnosis of GHD [61], particularly in obese children [62]. The overdiagnosis of GHD could be of great relevance, especially in view of a possible unjustified treatment with GH. However, considering the high burden of cardiovascular risk factors linked to low GH status, the evaluation of GH/IGF-1 axis could correctly identify different cardiovascular risk phenotypes among equally obese individuals, especially when the low GH secretion is paralleled by low IGF-1 levels.

6. Final steps along the road: potential GH treatment in obesity

There are considerable controversies about the potential use of recombinant human (rh) GH as an adjuvant therapy in a weight loss program for obese individuals. Indeed, no government-agency approved rhGH as pharmaceutic agents specifically for the treatment of obesity. Thus, to date, rhGH is not a standard-of-care to obese patients, moreover considering the side-effects of this therapy, including hyperglycemia. However, a large number of clinical and experimental studies show the favorable effects of rhGH treatment on body composition in obesity, also independently of weight loss, and suggest a true physiologic role of the GH/IGF-1 axis in mediating some of the co-morbidities associated with obesity. A recent review by Berryman [9] on the efficacy of rhGH therapy has evidenced only limited effects on weight loss in unselected obese individuals; nevertheless, this treatment has been effective in reducing total and visceral adiposity, increasing lean body mass, and improving lipid profile and glucose metabolism. Starting from these observations and emphasizing that further data are needed before rhGH administration can be recommended as standard-of-care to obese patients, three main issues arise in considering the clinical studies evaluating the effectiveness of GH as a treatment in the integrate management of obese individuals. These three issues can be arranged in a classic form of who–how–when questions. First, who is the target population of obese individuals. From a physiopathological point of view, it should be conceivable to limit the therapy to the specific subsets of obese individuals with abnormalities of the GH/IGF-1 axis, especially involving GH and IGF-1 simultaneously, in relation to their worse cardio-metabolic risk profile. Unfortunately, almost all the studies have been performed in unselected obese adults and to date no case–control studies have been available to compare the effectiveness of rhGH treatment in adequately large series of GH deficient and GH sufficient obese individuals. A careful investigation of GH/IGF-1 axis can represent an indispensable prerequisite in the evaluation of obese individuals assigned to rhGH treatment. The main criticism to GH treatment in obesity is that the low GH status could reverse after weight loss (8,51), although with some discrepancies (47). Nevertheless, as mentioned above, the recovery of GH and IGF-1 secretion might not be the rule after weight loss [8,47,49]. The second one is how to administer rhGH treatment properly. There is no general agreement on the effective dose of rhGH treatment in obese individuals. Many trials used relatively higher doses of GH compared to those recommended for adult GHD. Indeed, if the target population is the subsets of obese individuals with abnormalities of the GH/IGF-1 axis, then it would be logical to use rhGH replacement doses that normalize IGF-1 levels according to age and gender-specific values. This physiological regimen of rhGH replacement may also minimize the number of dose-related side-effects, such as hypertension, arthralgia, paresthesia and peripheral edema and reduce the unfavorable short-term effects on glucose metabolism, such as GH-induced hyperinsulinemia, which may oppose to the lipolytic effect of GH. Third, the duration of the treatment: rhGH treatment should be continued for a period of time sufficient enough to obtain along with weight loss the spontaneous recovery of GH/IGF-1 axis, if any, or until beneficial effects are evidenced. Indeed, improvements in glucose metabolism are observed only in long-term studies (>12 weeks) as the insulin-sensitizing effects due to the reduction in visceral adipose tissue and the increase in IGF-1 levels require a longer lap of time [63]. In addition, as reported in adult GHD, low dose-GH treatment might induce insulin-like effects through the increase in bioactive IGF-1 with a generation of IGF-1/insulin hybrid receptors at muscle levels [64]. Low dose rhGH replacement with normalization of IGF-1 levels may also be considered as an adjuvant therapy in preventing loss of fat free mass during the early post-operative period after bariatric surgery. In a randomized controlled study in morbidly obese females with persistent low GH/IGF-1 status after surgery, we have shown that rhGH replacement has resulted in a reduction in body weight mainly due to fat mass loss, with a significant sparing of lean body mass and improvements of lipid profile and insulin sensitivity [65]. Finally, a role for GHRH analogues increasing endogenous GH secretion, such as tesamorelin [66], has recently demonstrated to improve body composition without adversely affecting glucose metabolism, while studies on GH fragments with predominant antilipolytic activity have not yet yielded convincing results.

7. Conclusions

Obesity and somatotropic axis exhibit multiple and bidirectional relationships contributing to the multiple maladaptive endocrine changes involved in the pathogenesis of obesity. The low GH status in obese individuals is functional and almost reversed by weight loss; however, this condition is responsible for anthropometric and metabolic alterations increasing the cardio-metabolic risk profile. This hypothesis generates the following considerations: i) the different GH/IGF-1 axis status might be one of the mechanisms responsible for the heterogeneity in the obese phenotype; ii) although rhGH is not recommended as a standard-of-care to obese patients, many clinical studies show the usefulness of GH as an adjunctive tool in the treatment of the subset of obese individuals with reduced GH secretory capacity and low circulating levels of IGF-1, in relation to their worst cardio-metabolic risk profile; and iii) preoperatively testing the GH/IGF-1 axis in obese patients candidates for bariatric surgery may be useful in predicting the individual post-surgical outcome, while short term low dose treatment with rhGH resulting in normalization of IGF-1 levels has been proven to preserve fat free mass.

Authors' contribution

SS conceived the review and drafted the manuscript. CDS and LB contributed to drafting the manuscript. AC critically revised the text.

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