Growth Hormone & IGF Research 25 (2015) 59–65

Contents lists available at ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

Review

Effects of growth hormone–releasing hormone on visceral fat, metabolic, and cardiovascular indices in human studies

Takara L. Stanley, Steven K. Grinspoon *

Program in Nutritional Metabolism, Neuroendocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Article history:
Received 30 October 2014
Received in revised form 11 December 2014
Accepted 14 December 2014
Available online 20 December 2014

Keywords:
Growth hormone
Visceral obesity
Obesity
Growth hormone–releasing hormone
Cardiovascular risk

ABSTRACT

Increased visceral adipose tissue (VAT) is associated with reductions in endogenous GH secretion, possibly as a result of hyperinsulinemia, increased circulating free fatty acid, increased somatostatin tone, and reduced ghrelin. Reduced GH may, in turn, further exacerbate visceral fat accumulation because of decreased hormone-sensitive lipolysis in this depot. Data from multiple populations demonstrate that both reduced GH and increased VAT appear to contribute independently to dyslipidemia, increased systemic inflammation, and increased cardiovascular risk. The reductions in GH in states of visceral adiposity are characterized by reduced basal and pulsatile GH secretion with intact pulse frequency. Treatment with GH-releasing hormone (GHRH) provides a means to reverse these abnormalities, increasing endogenous basal and pulsatile GH secretion without altering pulse frequency. This review describes data from HIV-infected individuals and individuals with general obesity showing that treatment with GHRH significantly reduces visceral fat, ameliorates dyslipidemia, and reduces markers of cardiovascular risk. Further research is needed regarding the long-term efficacy and safety of this treatment modality.

1. Introduction

Beyond its effects on bone growth and musculoskeletal anabolism, growth hormone (GH) plays in important role in the regulation of lipid metabolism, body fat distribution, inflammation, and vascular health. These effects were first illustrated by data from individuals with frank GH deficiency (GHD) due to pituitary insufficiency. In 1990, Rosen and Bengtsson demonstrated that individuals with hypopituitarism had increased cardiovascular mortality compared to the general population [1]. As these individuals were receiving adrenal, thyroid, and gonadal steroid replacement but not GH replacement, Rosen and Bengtsson suggested that GHD might contribute to elevated cardiovascular mortality [1]. Further investigation in patients with GH deficiency has supported this hypothesis, demonstrating higher BMI, increased central adiposity, higher triglyceride (TG), decreased high-density lipoprotein (HDL), increased rate of hypertension, elevated inflammatory markers such as c-reactive protein (CRP), and increased carotid intima media thickness (cIMT) [2–6]. In further support of these findings, GH replacement in individuals with hypopituitarism increases muscle mass, decreases overall fat and visceral adiposity, improves dyslipidemia, reduces systemic inflammation, and decreases cIMT [3,7–11]. The benefits of GH replacement on body composition were first demonstrated by Jorgensen et al., who reported that GH treatment to normalize insulin-like growth factor 1 (IGF-1) in patients with GHD increased muscle volume and strength and decreased fat mass [10]. Subsequently, in the first randomized, placebo-controlled study of GH in adults with GHD, Jorgensen et al. demonstrated that GH treatment resulted in marked reductions in visceral fat in addition to the overall reductions in fat and improvements in muscle mass and muscle strength [11]. Further studies have shown not only improvements in body composition but also improvements in lipids and measures of cardiovascular health [3,7–11].

More recently, relative states of GH deficiency have been described in individuals with obesity, particularly those with increased visceral adipose tissue. As this review details, studies in viscerally obese populations have mirrored those in hypopituitary patients, demonstrating dyslipidemia, increased systemic inflammation, and increased cardiovascular risk in association with reduced GH secretion. These findings have prompted the investigation of strategies to augment growth hormone in viscerally obese individuals in order to ameliorate cardiovascular and metabolic risk. Recombinant human GH (rhGH) has shown some benefit in this regard [12–15] but has adverse effects on glucose homeostasis. This review will discuss an alternative strategy, the use of a GH-releasing hormone (GHRH) analogue to augment endogenous GH secretion in order to reverse the relative GH deficiency associated with visceral adiposity.

1.1. Obesity-related changes in the GH/IGF-1 axis

Both endogenous GH secretion and GH response to provocative testing are blunted in obesity [16–21]. Importantly, GH secretion is restored with weight loss, suggesting that the relative GH deficiency associated

* Corresponding author at: MGH Program in Nutritional Metabolism, LON5-207, 55 Fruit St., Boston, MA 02114. Tel.: +1 617 724 9109 ; fax: +1 617 724 8998.
E-mail address: sgrinspoon@partners.org (S.K. Grinspoon).

http://dx.doi.org/10.1016/j.ghir.2014.12.005
1096-6374/

with obesity is functional and reversible [21,22]. Whereas the inverse relationship between adiposity and GH secretion has been recognized for decades, visceral fat mass is now understood to be the most important determinant of reduced GH secretion in obesity. In a cohort of 42 healthy non-obese adults, Vahl et al. first demonstrated this link, showing intra-abdominal fat mass to be the dominant determinant of 24-h endogenous GH secretion [23]. Further studies have confirmed that visceral fat, rather than overall adiposity, is the measure of body composition most strongly associated with growth hormone secretion. In a cohort of non-obese women who underwent 24-h frequent sampling for GH concentrations, Miller et al. demonstrated that truncal fat was a strong independent predictor of 24 h mean GH, whereas total body fat and BMI were not significantly associated with GH [24]. Similarly, in a male cohort that underwent GH provocative testing, we demonstrated that measures of central adiposity—waist circumference, trunk fat by dual-energy x-ray absorptiometry (DXA), and visceral adipose tissue (VAT) measured by CT—were significantly associated with peak stimulated GH levels, whereas BMI was not associated with GH independent of measures of abdominal obesity [25]. In a multivariate model including waist and hip circumference, age, and BMI, peak GH decreased by 1.02 μg/L for every 1 cm increase in waist circumference ($p = 0.02$) [25]. In a separate model including age, BMI, and measures of abdominal fat area by single-slice computed tomography, peak GH decreased by 1 μg/L for every 10 cm^2 increase in VAT area ($p = 0.02$), whereas subcutaneous adipose tissue (SAT) and total adipose tissue area were not associated with peak GH [25]. The independent negative association between visceral adiposity and peak stimulated GH has also been demonstrated in adolescents [26].

Studies of endogenous GH secretion have shown that the number of GH pulses is not altered in obesity, whereas the magnitude of both basal and pulsatile secretion is significantly diminished [24]. Multiple mechanisms may contribute to reduced GH secretion in visceral obesity. In a study of men receiving a hypercaloric diet, Cornford et al. demonstrated that reductions in GH are strongly associated with increased insulin levels [27]. Moreover, decreased GH is seen within a few days of hypercaloric diet, temporally consistent with the increase in circulating insulin but before significant changes in body composition [27]. *In vitro* studies also support a role for insulin in the suppression of GH secretion, demonstrating that insulin decreases pituitary mRNA expression of GH, GHRH receptor, and ghrelin receptor [28,29]. Free fatty acids (FFA) also inhibit GH secretion [30]. In obese subjects treated with either placebo or acipimox, the latter of which inhibits lipolysis and decreases FFA, acipimox treatment resulted in significant increases in GH response to provocative testing [31]. Relative reductions in ghrelin and increases in somatostatin tone may also play a role in decreased GH secretion in states of visceral obesity.

Although GH is not reduced in all obese individuals, the rate of functional GH deficiency among obese individuals is substantial. In data from 302 men and women undergoing standard GHRH-arginine provocative testing in our unit, 29.4% of obese individuals met a strict definition of GH deficiency using a peak GH cutoff of 4.2 μg/L, determined by Corneli et al. to be an optimal cutoff for defining GH deficiency in obese individuals [32], (Makimura and Grinspoon, unpublished data). Similar prevalence of GHD—between 25% and 30%—has been reported in other obese cohorts [33,34]. Importantly, GH reductions in obesity are not consistently associated with reductions in IGF-1. Further, IGF binding protein 1 (IGFBP-1) levels are inversely associated with insulin levels and thus decreased in obesity, such that even obese individuals with reduced total IGF-1 may have normal or increased bioavailable IGF-1. Consequently, the consequences of reduced GH in obesity are likely due to the actions of GH itself, rather than those of IGF-1.

1.2. Metabolic correlates of relative GH deficiency in obesity

Obesity-related reductions in GH are significantly associated with measures of metabolic and cardiovascular risk. Multiple studies have demonstrated that both endogenous and stimulated GH secretion are positively associated with adiponectin and negatively associated with triglyceride, low-density lipoprotein cholesterol (LDL), c-reactive protein (CRP), and other markers of systemic inflammation [24,35]. These associations appear to be independent of overall adiposity [33,35,36]. Utz et al. demonstrated that women with obesity-associated GHD had higher serum concentrations of CRP and tumor necrosis factor receptor 2 (TNFR2) and lower high-density lipoprotein cholesterol (HDL) than women without GHD, even after controlling for BMI and a measure of central adiposity [33]. In a large cohort of men and women undergoing provocative GH stimulation testing, we have demonstrated that peak stimulated GH is inversely associated with LDL and HDL particle size, independent of adiposity and traditional cardiovascular risk factors, suggesting a more atherogenic lipoprotein profile in obese individuals with relative GHD [37]. Further, we have demonstrated that peak stimulated GH is independently negatively associated with cIMT in modeling controlling for traditional cardiovascular risk factors including smoking, lipids, glucose, and blood pressure [35]. In this cohort, obese individuals without reductions in GH had cIMT similar to normal weight controls, whereas obese individuals with relative GHD had higher cIMT (Fig. 1) [35], suggesting that reductions in GH may be an important mediator of the relationship between obesity and cardiovascular disease.

The adverse metabolic effects of increased visceral fat per se are also relevant to a discussion of GH and metabolic health, as GH deficiency is associated with increased visceral fat whereas therapy to augment GH significantly reduces visceral fat. Visceral fat accumulation is strongly associated with increased metabolic and cardiovascular risk [38–42], whereas subcutaneous fat, particularly that stored in the gluteofemoral region, appears to be beneficial with respect to metabolic health [43,44]. Specifically, VAT quantity is an independent risk factor for the development of diabetes, assessed prospectively, whereas neither BMI nor overall adiposity contributes to diabetes risk, and increasing lower body fat is protective against diabetes [45]. Additionally, VAT quantity is an independent risk factor of non-calcified coronary artery plaque and its progression over time, independent of known CVD risk factors [40,46]. Finally, VAT is also associated with overall mortality, independent of overall adiposity [47]. The importance of VAT in driving the metabolic comorbidities of obesity is highlighted by interventional studies of liposuction compared to omentectomy. Removal of subcutaneous fat through large volume liposuction has no benefit on blood pressure, lipids, or glucose [48,49], whereas omentectomy may result in improvements in glucose [50].

Together, the strong association between increased visceral fat and reduced growth hormone, and the contribution of both to metabolic perturbations and cardiovascular risk, may create a vicious cycle for some patients. Visceral fat accumulation may reduce GH secretion through multiple mechanisms, including increased insulin and FFA, decreased ghrelin, and increased somatostatin tone, whereas relative GH deficiency may, in turn, exacerbate visceral adiposity because of decreased hormone-sensitive lipolysis. Reduced GH appears to have independent adverse effects on cardiovascular and metabolic risk, as does visceral fat. Consequently, this self-reinforcing cycle of increased VAT and decreased GH may significantly contribute to cardiovascular and metabolic risk in states of visceral obesity (Fig. 2).

1.3. Rationale for the use of growth hormone–releasing hormone in obesity

Given the evidence suggesting an independent contribution of reduced GH to metabolic dysregulation and cardiovascular risk in obesity, a logical hypothesis is that augmenting GH in obesity may ameliorate these risks. Indeed, studies of rhGH treatment in obese individuals have demonstrated benefit, including decreased visceral fat and overall adiposity, increased lean mass, reductions in LDL and triglyceride, and reductions in CRP [12,13,15,51,52]. Most of these studies have also demonstrated worsening of glucose tolerance, however, with increased insulin and increased 2-h glucose levels following oral glucose tolerance