Chapter

Obesity: The Relationship between Growth Hormone and Exercises

Danubia da Cunha de Sá-Caputo, Mario Bernardo-Filho, Redha Taiar and Tecia Maria de Oliveira Maranhão

Abstract

Obesity is one of the main causes of death around the world. Moreover, considering the cardiometabolic risk (CMR), the relationship between obesity and CMR is well-established, and the location of adipose tissue (AT), particularly in the abdominal region, is considered an important predictor of metabolic dysfunction than total fat mass. Central obesity can be related to abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). The relationship between SAT and CMR is not still clear, but the VAT has been considered a unique pathogenic fat depot. In this context, it is important to identify clinical interventions that could be used to improve the management of obesity. The aim of this chapter is to integrate knowledge about the relevance of exercises and/or growth hormone (GH) to the management of individuals with obesity. In conclusion, it appears that exercise-induced reductions in VAT are mediated by induced changes in GH levels. This could be due to the similar lipolytic effects of both GH and exercise on VAT and this relationship would benefit the role of exercise as an intervention against obesity. Preventing and understanding the development of obesity is therefore essential if it is wanted to curb the global epidemic and save social security several million costs concerning health problems.

Keywords: obesity, growth hormone, exercise, abdominal subcutaneous adipose tissue, visceral adipose tissue

1. Introduction

Obesity is one of the main causes of death around the world. There has been a significant global increase in obesity rate during the last decades. This problem represents a global phenomenon occurring in all parts of the world region except parts of sub-Saharan Asia and Africa [1]. Moreover, this complex and undesirable clinical condition is a high- risk factor for various non-communicable diseases, such as, type 2 diabetes, cardiovascular disease, metabolic syndrome (MetSy), chronic kidney disease, hyperlipidemia, hypertension, nonalcoholic fatty liver disease, obstructive sleep apnea, osteoarthritis, and certain types of cancers [2, 3].

There are several possible mechanisms leading to obesity. The main cause is the significantly more excess energy stored in fat cells than the energy the body needs. This set characterizes the obesity disease [2, 4]. Research of Sacks et al. [5] showed

that the food sources and quality of nutrients matter more than their quantity in the diet contributes for weight imbalance. The pathogenesis of obesity involves regulation of calorie utilization, appetite and physical activity, but have complex interactions with availability of health-care systems, the role of socio-economic status, and underlying hereditary and environmental factors [6].

Considering the cardiometabolic risk (CMR), the relationship between obesity and CMR is well-established, and the location of adipose tissue (AT), particularly in the abdominal region, is considered an important predictor of metabolic dysfunction than total fat mass [7, 8]. In obesity, the central obesity (CO) is characterized by the excess accumulation of AT in the abdominal region. The CO is strongly and independently correlated with MetSy and is assessed through the measurement of the waist circumference (WC) [8, 9].

As it is indicated in **Figure 1**, CO can be related to abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) [10]. The relationship between SAT and CMR is not still clear, but, the VAT has been considered a unique pathogenic fat depot.

It is suggested that VAT would be a metabolic organ that would regulate fat mass, and glucose and nutrient homeostasis. VAT is also an active endocrine organ that synthesizes and secretes numerous bioactive mediators, adipocytokines/adipokines, and other vasoactive substances [11, 12]. These adipocytokines/adipokines act on various organs with metabolic importance, such as liver and skeletal muscle. There is evidence of the roles of adipocytokines/adipokines in the regulation of metabolic disorders like diabetes, obesity and insulin resistance. VAT is associated strongly with CMR independent of overall body mass index (BMI) or total body adiposity [13–15].

The growth of the economy in the world, mechanized transport, urbanization, industrialization, an increasingly sedentary lifestyle, and a nutritional transition to processed foods with high-calorie diets have favored the increase of the prevalence of obesity. Moreover, the rising prevalence of childhood obesity suggests a burden of this disease in the healthcare systems in the future [16].

In this context, it would be important to identify clinical interventions that could be used to improve the management of individuals with obesity. Considering that the relationship between CO and impaired growth hormone (GH) secretion, it is still poorly understood [17, 18], but the relevance of the exercise, as an intervention to improve the GH secretion has been highlighted [19–21].

Exercise and diet modification can be considered as therapies for the management of obesity. Verheggen et al. [19] reported that while exercise is less effective than diet for body mass loss, exercise would promote superior reductions in VAT. Moreover, Berryman and List [20] reinforce that this finding may partly be explained by exercise-induced changes in lipolytic hormones, such as GH, during and after exercise, which seem to target VAT.

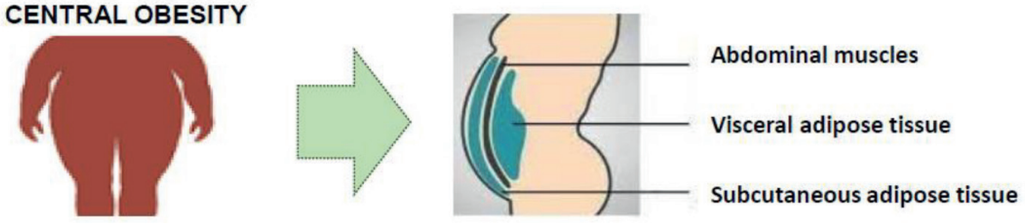

Figure 1.
Central obesity and subcutaneous and visceral adipose tissue.

Putting together these considerations, the aim of this chapter is to integrate knowledge about the relevance of exercises and/or GH to the management of individuals with obesity.

2. Growth hormone

GH is secreted at the anterior pituitary gland in a pulsatile manner and is primarily regulated by hypothalamic neuropeptides GH-releasing hormone and somatostatin, which stimulate and inhibit GH secretion, respectively [21]. It is known that resistance exercise (RE) is considered the most effective potent and physiological stimulus for GH release [22, 23], but little about how RE alters somatotroph content and function. Importantly, Rudman et al. [24] verified that when GH was administered to older healthy male, there were substantial decrease in AT mass, and significant increase in lean body mass. After that, studies have shown that GH therapy can improve VAT, circulating lipid levels, and insulin resistance in individuals with obesity and/or diabetes [15, 25]. In addition, it was observed the potential utility of GH therapy for the amelioration of age-related declines in metabolic function and body composition. GH is a potent anabolic hormone that affects multiple systems within the body and plays a significant role in lipid metabolism at various sites, such as liver, skeletal muscle, and AT [26]. Meanwhile, side effects of GH therapy such as an increased likelihood of soft tissue edema, joint pain, carpal tunnel syndrome, gynecomastia, hypertension, and diabetes have been reported [27, 28]. Considering these findings, exogenous GH therapy would became typically reserved for individuals with GH deficiencies resulting from hypothalamic/pituitary disease [29]. Despite this, there has since been increasing interest in identifying therapies, including lifestyle interventions, that increase physiologic GH release and action.

Considering the obesity, the somatotropic axis, that is a primary regulator of the metabolism, has particular relevance. The somatotropic axis consists of GH and insulin-like growth factors (IGF-I and IGF-II), and related to carrier proteins and receptors, which are further regulated by nutritional status and hormones such as ghrelin and insulin [30, 31]. During periods of fasting or stress, GH promotes the use of lipids as the primary fuel source in order to preserve carbohydrates and protein stores. In the liver, lipid uptake and production are increased through the phosphorylation of sterol regulatory element-binding proteins and by increased lipoprotein lipase (LPL) expression. In addition, GH also indirectly would increase the fatty acid oxidation and, additionally, would activate the adenosine monophosphate-activated protein kinase pathway [21].

GH is a powerful regulator of lipid metabolism, but its effect depends on the target. GH has lipogenic effects within the liver, however, the opposite occurs in AT, particularly VAT, where GH elicits lipolytic effects due to the suppression of LPL activity [17]. During exercise or fasting, GH stimulates the release of free fatty acids (FFAs) in the circulation to be delivered to various organs, including myocytes. In this case, FFAs may be repackaged as triglycerides or undergo β-oxidation in the mitochondria. While it is recognized that GH also elicits various effects on glucose and protein metabolism, exercise induced alterations in physiologic GH appear to primarily affect the AT lipolysis [32, 33].

Increased ectopic fat, such as VAT and intrahepatic triglyceride, contributes to insulin resistance and may affect the feedback control system of the somatotropic axis, resulting in a cascade of metabolic impairments [31].

3. Relationship between GH and exercise

Increases in GH secretion due to stress, such as fasting, or exercise contributes to lead increases in circulating FFAs [34]. Stokes et al. [35] showed that FFA levels may also regulate GH throughout a negative feedback control, as nicotinic acid-mediated suppression of lipolysis, and consequently reducing circulating FFAs, led to an important GH response. This finding may help further explain why individuals with obesity and reduced cardiorespiratory fitness (CRF), who on average have elevated levels of FFAs [36, 37].

Regular aerobic exercise enhances the ability of the body in the transportation and oxidization of FFAs during exercise [38]. This is also found in individuals with impaired fatty acid oxidation, such as those with obesity and diabetes [38-40], and it has been suggested that these improvements may be mediated through exercise-induced increases in mitochondrial and fatty acid transporter content, carnitine shuttle activity, and CRF [41, 42].

It is reported that low CRF may be a greater predictor of metabolic dysfunction than VAT [43], and as such, improving CRF has emerged as a therapeutic target for individuals with obesity-related disease. Moreover, acute exercise would temporarily increase the GH release, and such responses would be mediated by CRF [4]. Furthermore, although both aerobic and resistance exercise elicit a GH response, the relative contribution of aerobic exercise on GH response and action arguably is not totally understood. In this context, the evaluation of factors that contribute to aerobic exercise-induced GH response and how these changes influence VAT and cardiometabolic health more broadly have been studied [4].

GH promotes lipolysis within AT and increases mitochondrial oxidative capacity [44, 45] Although obesity decreases the exercise-induced GH response, CRF, which, at least, partly, is related to the muscle oxidative capacity, would be a more relevant determinant of exercise-induced GH secretion [4, 46].

Although the exercise and GH eliciting similar effects on AT and lipid metabolism, it is unclear whether exercise induced desirable effects in central adiposity are mediated by changes in physiologic GH response or if these effects in central adiposity and GH response are independent of exercise adherence [33, 47].

Acute aerobic exercise has been shown to increase GH levels, and these changes have been shown to be strongly associated with exercise intensity and volume, a function of exercise duration and frequency [48, 49]. It is suggested that exercise-induced GH responses may only be elicited at, or above, specific exercise volume and intensity parameters. Sasaki et al. [50] reported that with high-intensity interval training (HIIT) or moderate-intensity continuous training (MICT), the magnitude of GH response to exercise did not increase from pre-intervention measures in sedentary but otherwise healthy men for both interventions. Zhang et al. [51] reported, in a randomized controlled trial with young women with obesity, that when compared to energy-matched MICT, HIIT or supramaximal aerobic exercise led to greater VAT reduction but not greater changes from pre-intervention levels in serum GH measured immediately or 4 h after exercise. In fact, all groups showed elevated GH responses to exercise; however, only the higher-intensity interventions decreased VAT, suggesting that other factors likely contributed to these improvements. In addition, Calixto et al. [52] reported that the velocity of eccentric muscle action alters the acute responses following bench press exercises performed by resistance-trained men with a slow velocity leading to greater metabolic stress and GH response. Jørgensen et al. [53], previously, have pointed out that GH stimulates lipolysis and

lipid oxidation during basal and fasting conditions and investigated whether GH also regulates substrate metabolism during exercise. The GH-deficient individuals were studied during exercise with and without GH administration as compared to untreated healthy subjects. It was verified that the GH predominantly stimulated the turnover of free fatty acids in the recovery phase after exercise. Then, it is possible to verify that aerobic and anaerobic exercises influence of GH secretion [51–53] and, consequently, these exercises could have positive effects on the CO.

Whole-body vibration exercise (WBVE), used in systemic vibratory therapy [54], is a type of physical exercise. In the WBVE, mechanical vibration (MV) generated in the vibrating platform is transmitted to the body of an individual that is in contact with this platform. Some publications have reported that the WBVE can alter the release of GH [55–58]. The potential physiological effects of WBVE on various organs/tissues would be also related to possible neuromuscular responses and the tonic vibratory reflex [59–61]. Moreover, the interaction of the MV with the mechanosensory system would be also involved in the effects described by the WBVE. The mechanosensors in the body cells, once stimulated by the MV, modulate the biological activity through specific signaling pathways, such as releasing hormones, like GH, and other substances (e.g., amino acids, proteins, lipids, ions) [54]. In consequence, several biological effects might be observed in several organs and tissues due to the WBVE [59, 61]. Furthermore, it is relevant to highlight that WBVE, depending on the parameters used in the protocols of the interventions and posture, can be considered aerobic or anaerobic exercises [62, 63].

The mechanisms driving the exercise-induced improvements in cardiometabolic outcomes and the relation with the GH is not fully clear yet. But, due to the various metabolic impacts of the exercise and GH, it is presented in **Figure 2** a possible relationship among GH and exercise, VAT and obesity.

Like GH, exercise exerts potent lipolytic effects, particularly on VAT [59]. Furthermore, exercise elicits improvements in ectopic fat in the absence of body

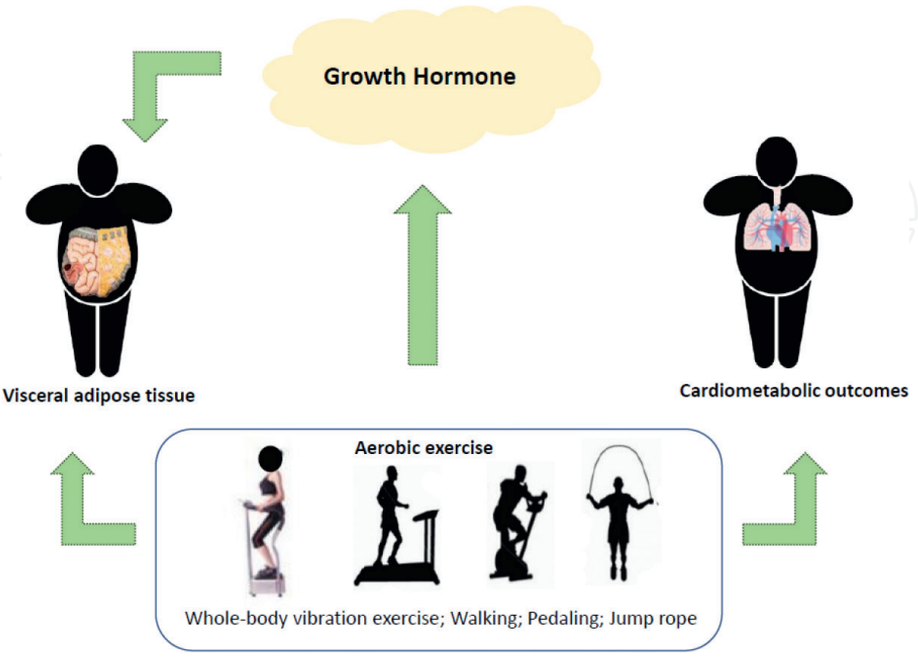

Figure 2.
The proposed relationship among growth hormone, physical exercises, adipose tissue, and cardiometabolic outcomes. Green lines represent positive effects from physical exercise to visceral adipose tissue.

mass loss [4]. As exercise induced GH response occurs in an intensity-dependent manner, and appears to be mediated by CRF, this may explain why HIIT can lead to similar improvements in WC and VAT than in higher-volume MICT despite requiring less time and expending less energy [60]. Moreover, considering the physiological adaptations and general health benefits of HIIT, individuals with obesity would be encouraged to perform such exercise.

4. Conclusion

In conclusion, it appears that exercise-induced reductions in VAT are mediated by induced changes in GH levels. This could be due to the similar lipolytic effects of both GH and exercise on VAT and this relationship would benefit the role of different types of exercises (aerobic and anaerobic exercises) as interventions against the obesity. Preventing and understanding the development of obesity is therefore essential, if it is wanted to curb the global epidemic and save social security several million costs concerning health problems.

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