ISSN 1809-9556

ARQUIVOS em MOVIMENTO
EEFD/UFRJ

FAPERJ
Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro

VOLUME 14, NÚMERO1
Janeiro/Junho2018

Hormônio do Crescimento e Exercício Físico

Daniele Leão Ignacio[1]&Flavia Lucia Conceição[2]

[1]Universidadede Brasília(UnB)–Departamento de Ciências Fisiológicas – Instituto de Biologia. Brasília - Brasil.
[2] Universidade Federal do Rio de Janeiro (UFRJ) – Departamento de Medicina Interna do Hospital Universitário Clementino Fraga Filho (HUCCF) – Divisão de Endocrinologia -Rio de Janeiro - Brasil.

Correspondência para: igdani18@gmail.com
Submetido em 6 de junho de 2018
Primeira decisão editorial em 13de junho de 2018
Aceito em 25 de junho de 2018

RESUMO
O exercício físico é um potente estímulo fisiológico para a secreção de GH, e tanto o exercício aeróbio quanto o exercício de força são capazes de aumentar a sua secreção. Entretanto, a idade, o sexo, o nível de aptidão física e o percentual de gordura são fatores que interferem na secreção de GH em resposta ao exercício. Existe uma relação linear entre intensidade do exercício aeróbio e magnitude de aumento do GH. Em relação ao exercício de força, é importante controlar o tempo de intervalo entre as séries, a carga e a frequência da sessão de treino para que ocorra aumento de GH. O eixo GH/IGF-1 exerce efeitos metabólicos a curto e a longo prazo que são importantes durante e após o exercício, como por exemplo a regulação do metabolismo de substratos, favorecendo a mobilização de ácidos graxos livres do tecido adiposo para a geração de energia, aumentando a oxidação da gordura e o gasto energético. O exercício regular também pode aumentar a taxa de secreção de GH durante 24h, contribuindo para as adaptações ao treinamento. Os efeitos da reposição de GH em pessoas que apresentam deficiência deste hormônio mostram diversos efeitos relacionados a melhora da composição corporal e da capacidade física, porém nem sempre esses efeitos podem ser vistos em sujeitos saudáveis e muito menos traduzidos em performance física. Mesmo assim, o abuso de GH no meio esportivo profissional e por entusiastas da atividade física não é algo incomum. Sendo assim, esta revisão pretende mostrar: 1) as evidências sobre a influência do exercício físico aeróbio e de força, tanto agudo quanto crônico, na secreção de GH; 2) descrever os mecanismos que regulam a secreção fisiológica de GH e que podem influenciar na resposta da secreção do GH ao exercício; 3) abordar os efeitos do GH no metabolismo em repouso e durante o exercício e 4) entender os motivos que justificam seu uso e abuso por atletas e entusiastas da atividade física.
Palavras-chave:GH/IGF-1, Exercício Físico, Respostas ao exercício agudo e treinamento.

Growth Hormone and Physical Exercise

Daniele Leão Ignacio[1]&Flavia Lucia Conceição[2]

[1] Universidade de Brasília (UnB) – Departamento de Ciências Fisiológicas – Instituto de Biologia. Brasília - Brasil.
[2] Universidade Federal do Rio de Janeiro (UFRJ) – Departamento de Medicina Interna do Hospital Universitário Clementino Fraga Filho (HUCCF) – Divisão de Endocrinologia - Rio de Janeiro - Brasil.

Correspondence to:igdani18@gmail.com
Submitted in June6th, 2018
First editorial decision in June13th, 2018
Accepted in June25h 2018

ABSTRACT

Physical exercise is a potent physiological stimulus for GH secretion, and both aerobic and strength exercise are able to increase its secretion. However, age, sex, physical fitness levels and fat percentage are factors that interfere with GH secretion in response to exercise. There is a linear relationship between aerobic exercise intensity and magnitude of GH increase. In relation to the strength, it is important to control the interval time between the series, the load and the frequency of the training session in order to increase GH. The GH / IGF-1 axis exerts short-term and long-term metabolic effects that are important during and after exercise, such as regulation of substrate metabolism, driving the mobilization of free fatty acids from adipose tissue for energy generation, increasing fat oxidation and energy expenditure. Regular exercise can also increase the rate of GH secretion for 24 hours, contributing to adaptations to training. The effects of GH replacement on people who are deficient in this hormone show several effects related to improvement of body composition and physical capacity, but not always these effects can be seen in healthy subjects, much less translated into physical performance. Even so, GH abuse in the professional sports environment and by physical activity enthusiasts is not uncommon. Thus, this review intends to show: 1) the evidence on the influence of aerobic physical exercise and both acute and chronic strength exercise on GH secretion; 2) describe the mechanisms that regulate the physiological secretion of GH and that can influence the response of GH secretion to exercise; 3) to address the effects of GH on resting and exercise metabolism and 4) to understand the reasons that justify its use and abuse by athletes and physical activity enthusiasts.

Keywords:GH/IGF-1, Physical Exercise, Responses to exercise

INTRODUCTION

Growth hormone (GH) is a 191 amino acid single chain peptide produced and secreted by a type of endocrine cell called the somatotroph, which is located in the anterior portion of the pituitary gland, which is a gland located at the base of the brain (Davidson 1987). Physical exercise is a potent stimulator of GH synthesis and secretion and several training methodological variables, such as intensity, volume and frequency (Mulligan et al., 1996), regulate GH secretion after exertion. However, some physiological aspects still remain controversial, including factors that regulate its synthesis and effects on the metabolism of substrates. Even so, GH abuse is large on the part of athletes and physical activity practitioners, probably because it is believed that the effects observed in people with GHD (growth hormone deficiency) can be extrapolated to healthy individuals and translated into increases in performance (Graham et al., 2008).

Thus, this review aims to show the evidence that exists in the literature on the influence of aerobic physical exercise and both acute and chronic GH secretion, describe the mechanisms that regulate the physiological secretion of GH and that can influence in the GH secretion response to exercise. In addition, the reasons that justify the use and abuse of GH by athletes and physical activity enthusiasts will be addressed.

THEORETICAL FOUNDATION

Growth Hormone - Mechanism of Action

Hormones bind to cognate receptors to exert their biological effects (Fig. 1). In the case of GH, signaling occurs after binding to its receptor (GHR), which belongs to class I of the cytokine receptor superfamily, located on the plasma membrane of target tissues (Brooks and Waters 2010). As a result, activation of the adjacent molecule Janus kinase 2 (Jak 2), a protein with tyrosine kinase activity present in the cytoplasm, is associated with GHR. Once activated, Jak 2 phosphorylates the GHR tyrosine residues, which in turn recruit members of the STAT family, which are signal transducing and transcription activating proteins. STAT5b has been extensively associated with GH actions, although others are also recruited by phosphorylated GHR (1, 3 and 5a) (Smit et al. 1996). The phosphorylation of STATs by Jak2 results in their receptor dissociation (Hansen et al., 1996), dimerization and translocation to the nucleus where it will bind to DNA in GH responsive gene promoter regions to regulate its transcription (Herrington and Carter-Su 2001), such as insulin-like growth factor-1 (IGF-1), acid labile subunit (ALS) and suppressor cytokine signaling (SOCS, suppressor of cytokine signaling). SOCS proteins are a family of negative regulators that, among other functions, are responsible for the inhibition of the GH signaling cascade (Hansen et al., 1996) (Figure 1). Phosphotyrosine phosphatases also regulate the pathway negatively (Stofega et al., 2000). In parallel to the Jak2 / STAT pathway, GHR can also bind Src tyrosine kinase and activate other alternative lanes of signaling (Lanning and Carter-Su 2007). GHR is widely expressed in the liver, kidney, adipose tissue, intestine, lung, pancreas, cartilage and skeletal muscle (A. Giustina, Mazziotti, and Canalis 2008). GH circulates in both free and bound forms, and the GH binding protein is called GHBP (GH-binding protein) (Amit, Youdim, and Hochberg 2000). In humans, GHBP is generated by proteolytic cleavage of the GHR extracellular domain (Clark et al., 1996); already in rodents, is derived from alternative GHR mRNA splicing (Amit, Youdim, and Hochberg 2000). GHBPs are synthesized primarily in the liver, although extrahepatic tissues, such as muscle and adipose tissue, contribute to circulating levels of GHBP (Leung et al., 2003). Serum

levels of GHBP serve as a marker of GH receptor (GHR) expression and GH responsiveness in a given tissue (Amit, Youdim, and Hochberg 2000). The role of GHBPs is not yet fully understood, although their role in modulating GH activity is known, either by prolonging their half-life or reducing the possibility of interaction with GHR (Baumann, Amburn, and Shaw 1988).

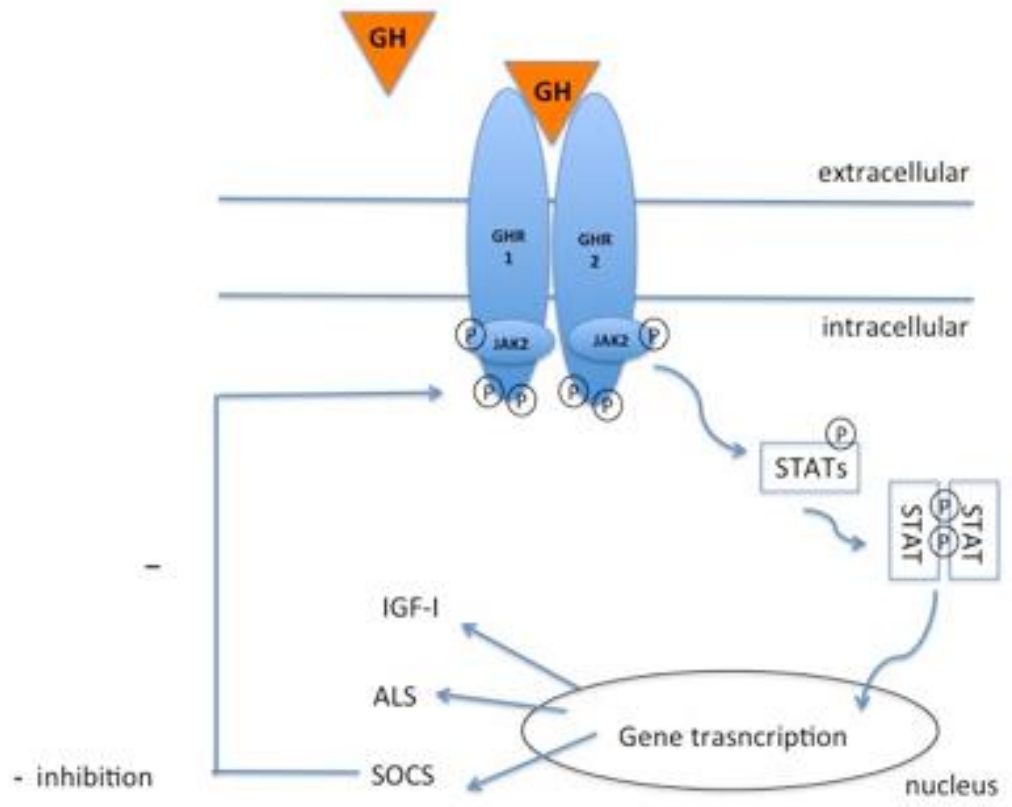

Figure 1 - Mechanism of action of growth hormone.

Neuroendocrine regulation of the GH / IGF1 axis

At the central level, 3 regulatory neuropeptides control the secretion of GH, they are: growth hormone releasing hormone (GHRH), somatostatin and the acylated form of the endogenous peptide ghrelin, secreted and produced by the stomach and in several other tissues, including the hypothalamus (Giustina and Veldhuis 1998; Ferrini et al., 2009). (Fig. 2) The neuroanatomic localization of GHRH and somatostatin and functional evidence suggest bidirectional synaptic interaction between the two peptidergic systems (Muller, Locatelli, and Cocchi 1999). GHRH stimulates the synthesis and secretion of GH, since somatostatin inhibits the secretion of GH directly in the somatotrophs, there is not inhibitory effect on the synthesis. Ghrelin, as well as analogous synthetic peptides known as GH secretagogues (GHS) or GH releasing peptides (GHRPs), may act synergistically with GHRH by stimulating pituitary secretion of GH (Pritzlaff-Roy et al., 2002). Somatostatin also antagonizes the secretagogue

activity of ghrelin GH, also antagonizes GHRH secretion and inhibits ghrelin secretion by the stomach (Farhy, Bowers, and Veldhuis 2007).

The GH-IGF1 axis is supported by negative feedback mechanisms of circulating GH and IGF-1, on IGF-1 we will speak later (Veldhuis et al., 2001). The regulation of feedback occurs at the hypothalamic level through GH and pituitary through IGF-1, although its action in promoting feedback also occurs at the hypothalamic level (Figure 2). Metabolic factors also trigger negative feedback, such as: glucose and free fatty acid (Baumann 2012b).

GH secretion occurs pulsatile in men and women, with the highest peak occurring at the onset of slow-wave sleep (stage IV) (Hartman et al., 1991), however, the presence of a pulse is characteristic of the male secretion pattern dominant night. In women, GH secretion is more continuous and irregular, with pulses of similar amplitude 24 hours a day (Jaffe et al., 1998; Pincus et al., 1996). In addition, women have higher basal serum concentrations of GH when compared to men, as well as higher concentrations of GH for 24 hours (KY Ho et al., 1987; L Wideman et al., 1999). However, women are less responsive than men to GH treatment, resulting in lower IGF-1 production in response to GH (Burman et al., 1997), but the mechanism involved is poorly understood.

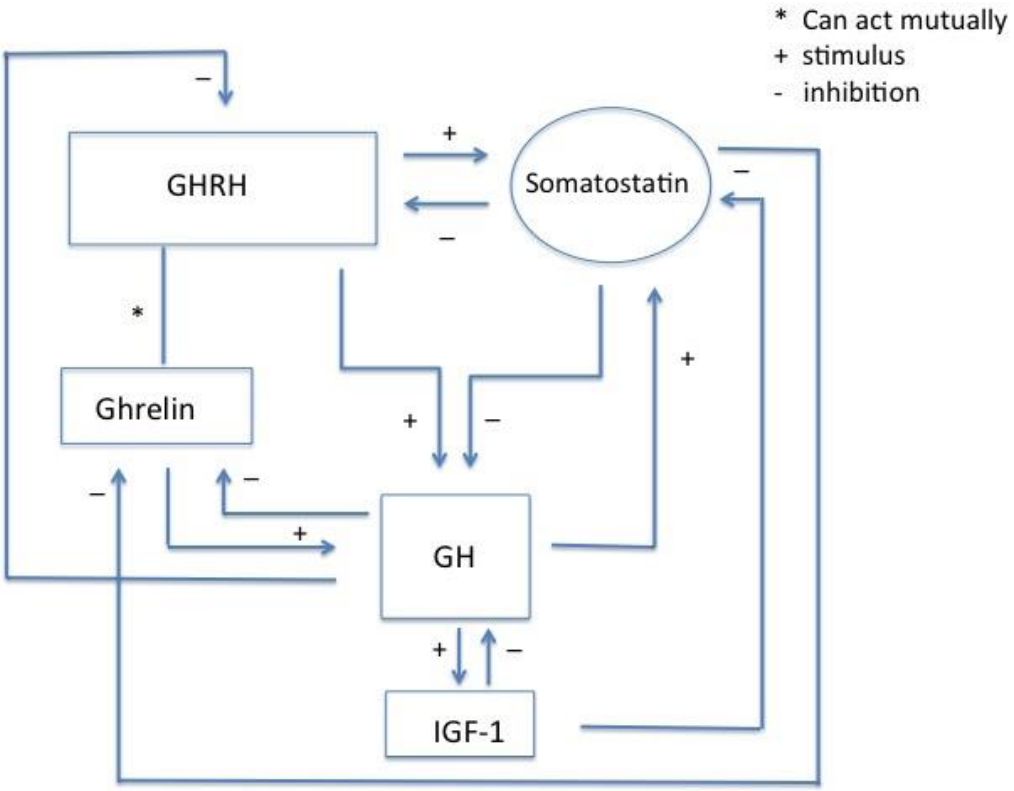

Figure 2 - Regulation of GH secretion.

Other factors regulating the GH/IGF1 axis

In addition to the interaction of the main regulatory neuropeptides mentioned above, some neurotransmitters, circulating hormones and other factors modulate GH secretion (Giustina and Veldhuis 1998).

GH secretion peaks during adolescence and declines by about 14% per decade from the age of 30, so sexual steroids are important positive regulators of GH secretion. In addition, thyroid hormones play an essential role in the synthesis and secretion of GH. Thyroidectomy in rats causes a decline in the pituitary GH content and thyroid hormone replacement therapy reverses this effect (Solomon and Greep 1959). In children with hypothyroidism, thyroid hormone replacement improves GH response to various stimuli (Katz et al., 1969). Acute glucocorticoid administration stimulates GH secretion, but when administered chronically inhibits. Exposure to supra-physiological glucocorticoid doses also slows growth, as observed in Cushing's syndrome (Rosenfeld 2005).

A series of neuropeptides and neurotransmitters are involved in regulating the secretion of GH acting at the hypothalamic level via somatostatinergic neurons and via GHRH (Fanciulli, Delitala, and Delitala 2009). A2- adrenergic neurons stimulate, while ¤1 and þ2 inhibit GH secretion (Ghigo et al., 1990). Dopaminergic pathways cause an acute increase in GH secretion (Vance et al., 1987). Cholinergic transmission is involved in GH secretion, as a cholinesterase inhibitor known as pyridostigmine, stimulated basal GH secretion, and increased the GH response to some secretagogues (Müller, Locatelli, and Cocchi 1999). There seems to be also a stimulatory role for histamine and serotonin in GH secretion (Fanciulli, Delitala, and Delitala 2009). Endogenous opiates and opioids stimulate GH secretion in animals. In humans, administration of an enkephalin analog leads to increased release of GH (Stubbs et al., 1978). Galanin, a neuropeptide present in the hypothalamus, increases GH secretion, and increases the GH response to GHRH in healthy men (Giustina and Veldhuis 1998). Amino acids are also capable of increasing GH secretion, the most potent amino acid arginine being. All these stimuli appear to be mediated by hypothalamic somatostatin, via reduction of their suppressor tone in the hypothalamus (Ghigo et al., 1990).

Glucose levels in the bloodstream, as well as free fatty acids, regulate GH secretion. In men, hyperglycemia causes transient suppression of GH for 1-3 hours, followed by increase 3-5 hours after glucose infusion. On the other hand, hypoglycemia increases the secretion of GH (Goldenberg and Barkan 2007), but repeated periods of hypoglycemia reduce GH secretion in response to a new stimulus (Oliver et al., 2010). Interestingly, overweight individuals undergoing 25% caloric restriction did not increase GH secretion, but GH was able to increase when they combined caloric restriction and exercise (Redman et al., 2010).

Much used in the clinic and considered gold standard, the insulin test to assess GH secretion is based on this principle, since insulin infusion is able to rapidly decrease serum glucose levels. Finally, elevation of free fatty acids is a strong inhibitor of the release of GH in humans and conditions that can generate chronic elevations of free fatty acids, such as obesity, can suppress GH secretion (Goldenberg and Barkan 2007). On the other hand, antilipolytic agents, such as acipimox, capable of significantly reducing serum levels of free fatty acids, stimulate GH secretion in obese individuals (Kreitschmann-Andermahr et al., 2010).

In addition, several physiological factors modulate GH secretion, such as: age, sex, nutrition, sleep, body composition, sex steroids, insulin and level of physical conditioning (Laurie Wideman et al., 2006). It is important to emphasize that obesity, especially visceral fat increase, is an important negative regulator of GH secretion, whereas physical conditioning,

evaluated by maximal oxygen consumption (VO2max), is one of the main positive determinants of GH secretion (N Vahl et al., 1996).

Insulin-like growth factor (IGF-1)

In the past GH was considered to exert its effects only through the generation of IGF-1 by the liver, to this discovery was given the name of "somatomedin hypothesis" (Denko and Bergenstal 1955). Over time this original hypothesis evolved giving rise to "dual effect theory", proposing an alternative form of regulation in which GH would exert its effects directly on target peripheral tissues or through IGF-1, which could be produced both by the target tissues, and by the liver in response to GH action (Green, Morikawa, and Nixon 1985). GH, in addition to stimulating hepatic IGF-1 synthesis, is now known to stimulate the formation of the IGF-binding ternary complex, which includes the acid labile subunit (ALS) and IGFBP- 3 (insulin-like growth factor binding protein-3), whose main function is to stabilize serum IGF. Nowadays, somatic growth is known to be due to both the endocrine production of IGF-1 and the autocrine and paracrine local action of the GH / IGF-1 system. Moreover, evidence points to important effects of GH-independent IGF-1 (Ewton and Florini 1981; Florini, Ewton, and Coolican 1996).

Biological effects of GH

GH has effects that are evident during adolescence, but in adulthood it continues to be responsible for several important metabolic actions. The summary of its biological effects is shown in Figure 3.

There are GH actions that may also be independent of IGF-1, such as its lipolytic, hyperglycemic actions and sodium homeostasis. GH administration causes hyperinsulinemia and prevents the suppressive action of hepatic glucose production by insulin, also inhibiting the action of insulin on glucose uptake and oxidation (K. K. Ho, O'Sullivan, and Hoffman 1996).

GH is hyperglycaemic, this leads to increased insulin. To exert this effect (hyperglycaemic) it acts on muscle, adipose tissue and liver. In muscle and adipose tissue GH prevents the uptake and oxidation of glucose, this effect is antagonistic to that of insulin. In the liver it also antagonizes the actions of insulin, as it increases the production of hepatic glucose through the increase of glycogenolysis and gluconeogenesis (Ghanaat and Tayek 2005; Kaplan et al. 2008), further contributing to the hyperglycemic effect and leading to insulin to try to reduce blood glucose (Sperling, 2016). On the other hand, GH also controls the production of IGF-1 that has insulin-like effects on metabolism (Vijayakumar et al., 2010). Thus, GH promotes insulin resistance, but only affects the metabolism of carbohydrates. In relation to protein metabolism, GH promotes a positive nitrogen balance, stimulating protein synthesis in the muscle.

Lipolysis is stimulated in adipose tissue by GH and this effect contributes to the savings of glucose and amino acids (Sperling, 2016). In addition, the lipolytic effects of GH are more pronounced in visceral adipose tissue and to a lesser extent in subcutaneous adipose tissue (Freda et al., 2008). GH also causes sodium retention that occurs in part by the activation of the renin-angiotensin system (K. K. Ho, O'Sullivan, and Hoffman 1996). All these effects are direct effects exerted by GH.

Reductions in strength and exercise tolerance can be explained because lean mass is decreased in GHD patients, and it is difficult to safely determine the reduction of lean mass in these patients or the increase with GH replacement because the reduction in total body water is evident in patients with GHD and the increase can occur in patients who do replacement, so that

lean mass can be overestimated due to the degree of tissue hydration (Monson, Brooke, and Akker 2000).

GH stimulates longitudinal growth inducing chondrocyte proliferation and differentiation of the long bone growth plate, this effect is evident during adolescence, so that sex steroids also contribute significantly to bone growth at this stage of life, interacting strongly with the GH / IGF-1 axis in the determination of skeletal maturation and skeletal sexual dimorphism (Callewaert et al., 2010; Mauras and Haymond 2005). GH also induces osteoblast proliferation, type I collagen synthesis, and collagenase 3, a protease that degrades collagen, through an IGF-1 dependent process (Le Roith et al., 2001). The GH / IGF-1 axis is able to promote erythropoiesis in vitro (Golde, Bersch, and Li 1977) in animal models (Kurtz et al., 1988) in growing children (Vihervuori et al., 1996) and in children with GHD after long-term treatment with GH (A. Esposito et al., 2016). Treatment with GH reduced the time to restore phosphocreatine in skeletal muscle, suggesting a local paracrine effect of IGF1 on mitochondrial function, since phosphocreatine is restored aerobically. IGF-1 expression in skeletal muscle, not blood, was directly related to mitochondrial function (Hamarneh et al., 2015).

GH is important for the proper functioning of the myocardium, affecting both its structure and its function. GH deficiency decreases left ventricular mass, these effects may be direct or via IGF-1 (Colao 2008). The decrease in left ventricular function is common in GHD patients, this is due to the reduction of total body sodium, with consequent decrease of extratecidual water, being this an important factor that reduces the physical capacity. (Monson, Brooke, and Akker 2000).

GH seems to play an important role in the control of thermoregulation. The rate of sweat secretion in adult patients with GHD is significantly lower compared to normal people and increases after GH replacement (Widdowson et al., 2009). GH increased in sequenced running and cycling activities one after the other and was able to increase plasma volume by decreasing sweating (Galy et al., 2014). In the kidneys, the GH / IGF-1 axis exerts antidiuretic and antinatriuretic effects, in addition to decreasing potassium excretion (Auriemma et al., 2010).

The immune system is also the target of GH action, and an important role of GH is the maintenance and function of the immune system, being able to act in the lymphoid compartments of the thymus and in peripheral lymphoid organs (Smaniotto, Martins-neto, and Dardenne 2011).

In addition, GH also acts on the central nervous system triggering neuroprotective and antiapoptotic effects possibly independent of IGF-1. However, the effects of cell proliferation and differentiation in the adult brain promoted by IGF-1 have been studied more broadly. GH and IGF-1 improve cognitive function, sense of well-being and memory. This is perceived in GH subjects undergoing supplementation with GH and in animal experiments. But it is important to emphasize that this happens only in symptomatic GHD patients, since in people with GHD who do not present GH seems to have no effect (Aberg, Brywe, and Isgaard 2006). This is realized in GH subjects undergoing supplementation with GH and in animal experiments. But it is important to emphasize that this happens only in symptomatic GHD patients, since in people with GHD who do not present GH seems to have no effect (Aberg, Brywe, and Isgaard 2006). All biological effects are summarized in Fig. 3.

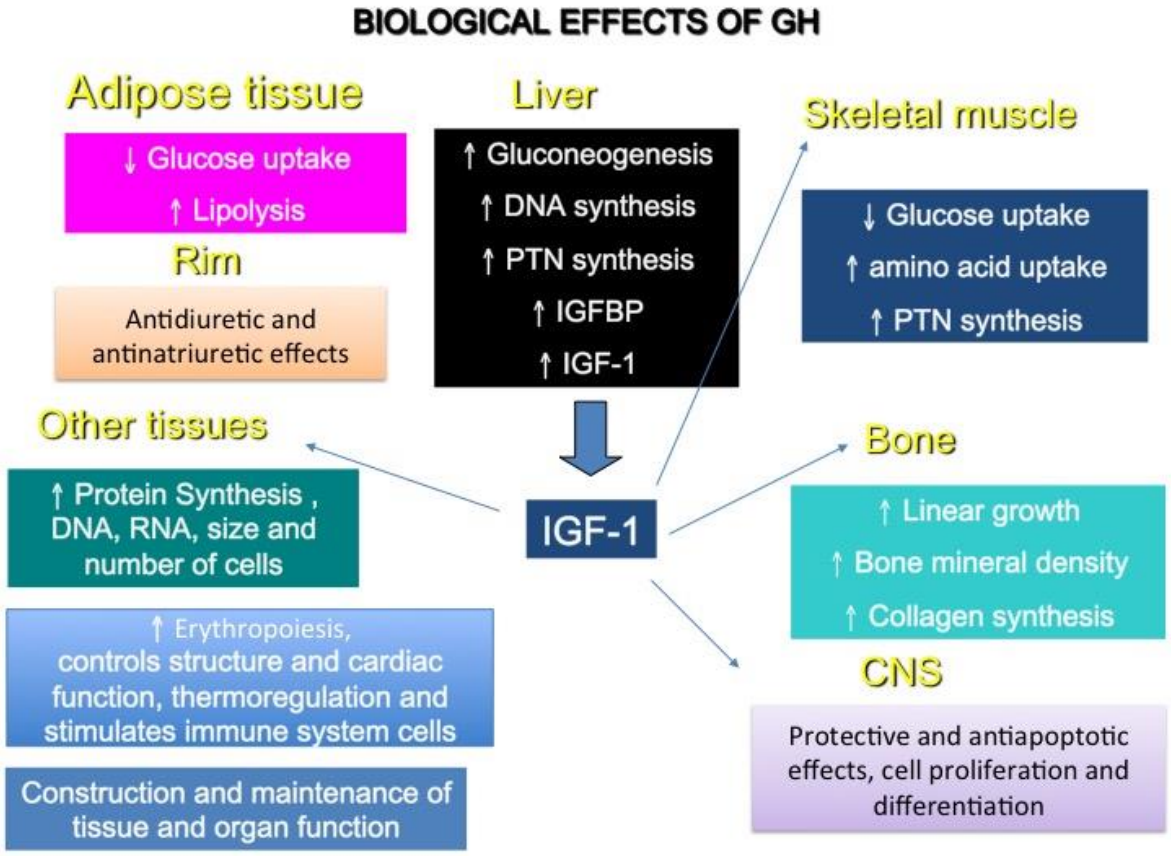

Figure 3 - Biological effects of GH. GH has direct actions in some tissues and in others it can act via IGF-1 (thin blue arrows). Abbreviations: DNA- deoxyribonucleic acid, IGFBP-insulin-like growth factor binding protein, IGF-1 insulin-like growth factor, PTN-protein, RNA-ribonucleic acid, CNS-central nervous system.

PRACTICAL APPLICATION

GH and exercise

Physical exercise is a potent physiological stimulus for the secretion of growth hormone (GH) in humans (Laurie Wideman et al., 2002a). The metabolic effects exerted by the GH / IGF-1 axis that occur in the short and long term lead to changes that are important during exercise.

Evidence shows that the acute increase of GH is important to regulate the use of metabolic substrates during an exercise session. While physical training also leads to changes in the GH / IGF-1 axis that contribute to the adaptations resulting from a regular exercise program (Widdowson et al., 2009). In this session, it will be discussed how the GH responds to the aerobic exercise and of strength, both acute and chronic and on some variables that interfere in its secretion.

Acute aerobic exercise

Both low intensity and long duration exercise, such as high intensity and short duration exercise, result in acute increases in GH secretion (Laurie Wideman et al., 2002a). GH levels begin to increase 10 to 20 minutes after exercise, with the peak occurring at the end or shortly after the end, and can remain high up to two hours after the end (Lassarre et al., 1974; Viru, Karelson, and Smirnova 1992).

The GH response to exercise depends on the gender (L Wideman et al., 1999; Giannoulis et al., 2006), age (R. IG Holt et al. (Laurie Wideman et al., 2006), intensity (Pritzlaff et al., 1999) and type of exercise (Felsing et al., 1992). A moderate-intensity exercise session at approximately 65% of maximum oxygen consumption lasting at least 20 minutes is sufficient to trigger a GH response (Hartley et al., 1972).

Some studies have shown that in order to have a substantial increase in GH secretion, the intensity of the aerobic exercise should be above the lactate threshold (Felsing et al., 1992; Chang et al., 1986). Pritzlaff et al. (1999) developed a study in which men performed acute exercise at 5 different intensities, with each individual normalized by their lactate threshold. GH response increased as the intensity increased. Later, studies from the same laboratory showed that when intensity is constant, GH secretion depends on duration (Laurie Wideman et al., 2006) and that repeated exercise sessions positively influence GH secretion (JA Kanaley et al. 1997).

However, contrary to previous studies that show that it is necessary to reach a threshold of intensity to have an increase in GH secretion, a study developed by Wideman et al. (2006) showed that regardless of age and sex, there is a linear relationship between intensity and an acute increase of GH.

In order to compare the secretion of GH in men and women at rest and during exercise, Wideman et al. (1999) used men and women of the same age and and observed the following: women increased GH secretion before men and had higher secretion rates at baseline; however, during exercise, although they reached higher absolute values than men, the magnitude of response was equal. This fact has been confirmed in later studies (Giannoulis et al., 2006).

GH response to exercise decreases with increasing age (Zaccaria et al., 1999a), and it is difficult to separate the inherent characteristics of aging from effects on body composition, for example. In a study designed to separate the effects of age, body composition and physical capacity and try to point out which would be the most contributory factor to the decreased GH response, Holt et al. (2001) compared 4 groups: lean/young men, overweight/young, lean/elderly and elderly/overweight. As a conclusion, they found that the GH response is determined by age and physical capacity (VO2max), but not by body fat, and it is more important with the advancement of age to maintain physical capacity than to adiposity to maintain a better secretory response of GH. However, programs that improved the physical capacity of people with obesity did not provide increases in GH response to exercise (Zaccaria et al., 1999a, J. Kanaley et al. Obesity (in particular the increase in visceral adipose tissue) is an important factor leading to the decline of GH levels in the elderly (Nina Vahl et al., 1997). In children and adults with obesity, there is a significant reduction in GH secretion. The higher the body mass index (BMI), the lower the GH response to certain stimulus tests, such as physical exercise (J. a Kanaley et al., 1999). In addition, GH secretion blockade in response to exercise occurs in obese children in both the early and late stages of puberty (Oliver et al., 2010).

Both continuous and intermittent exercise are effective in increasing GH secretion for 24 hours, but basal secretion and pulsatile GH secretion has been attenuated both at rest and during exercise in obese individuals. In obese individuals, improvement in physical fitness was

not able to prevent the inhibitory effect of GH secretion in individuals with high BMI and probably visceral adipose tissue, so to increase GH secretion an appropriate exercise program that induces weight loss should be encouraged to reduce visceral adipose tissue (Arthur Weltman et al., 2008).

Acute exercise affects other components of the GH / IGF-1 axis. Schwarz et al. (1996) subjected adult men to a short-acting acute exercise session (10 minutes) in two different light and intense intensities and observed increased IGFBP-3 proteolysis, as well as increased serum concentrations of IGF-1 and IGF-2 at both exercise intensities. These effects preceded the GH peak, showing that IGF secretion did not depend on GH during exercise, which only increased with high intensity. The physiological significance of these changes has not yet been elucidated.

The sympathetic activity is an important mediator of the GH response to acute exercise, through activation of the alpha2 adrenergic receptors (A Weltman et al., 1997). The GH response to exercise is attenuated in obese women compared to non-obese women and this is due to the lower mass of GH secreted per pulse in obese women (J. a Kanaley et al. The mechanisms are still unclear, but cholinergic (Brillon, Nabil, and Jacobs 1986) adrenergic pathways (Arthur Weltman et al., 2000), endogenous opioids (the most important enkephalin) (Miki, Ono, and Shizume 1984), central temperature (Christensen et al., 1984; Wheldon et al., 2006) and pH appear to be involved. There are few studies in the literature showing the effects of pH, although one study has shown a reduction in GH secretion in response to the alkaline infusion (Elias et al., 1997).

Evaluating the physiological mechanisms involved in increasing GH after different types of exercise is important because of the phenotypic differences that each cause (Laurie Wideman et al., 2002b). In this sense, with the purpose of evaluating the mechanisms that lead to GH secretion post-exertion, Ignacio et al. (2015) analyzed in ovariectomized rats (surgical procedure of ovarian withdrawal that simulates a state of low levels of estrogen in humans) the effect of a session of 20 minutes of treadmill exercise to 75% of the maximum aerobic capacity in GH secretion. In this model, it was shown that 30 minutes after the end of the exercise the level of GH in the blood was higher in the group that presented normal estrogen level. In order to analyze the physiological mechanisms that lead to GH secretion after exertion, the influence of thyroid hormones has also been investigated, since thyroid hormones play an essential role in the control of GH synthesis and secretion, so that thyroidectomy in rats causes a decline in the content pituitary GH and thyroid hormone replacement therapy reverses this effect (Solomon and Greep 1959; Coiro et al., 1979). Similarly, in children with hypothyroidism, thyroid hormone replacement improves GH response to various stimuli (Brauman and Corvilain, n .; Katz et al., 1969). However, we did not know how post-effort regulation occurred. Interestingly, it has been shown that the estrogen deficiency induced in rats by ovariectomy prevented the activation of the enzyme deiodase type 1 that converts the prohormone T4 into T3, regulating the gene expression of GH in the pituitary gland. The release of GH was also lower in this group. In order to evaluate whether there were a cause and effect relationship between these two factors (activation of type 1 deiodase and GH secretion), pharmacological blockade of this enzyme was performed in intact animals and these animals were submitted to the same acute exercise session, which blocking the secretion of GH post-exercise, suggesting that in rats, there is a permissive role of thyroid hormones in the release of GH post-exertion mediated by type 1 deiodase in the pituitary gland (Ignacio et al., 2015).

Inorganic nitrate, the end product of nitric oxide metabolism, was seen as an inert metabolite, but today there is evidence of improvement of various aspects related to exercise after consuming it through diet (Lundberg et al., 2011; Cermak, Gibala, and van Nitrate induces responses that mimic physical exercise (Roberts et al., 2017), for example, increased expression

of PGC1a in skeletal muscle and regulation of type IIb (rapid contraction) muscle fiber exchange for type I (slow contraction) and IIa (intermediate) (Ashmore et al., 2015). In the work of Roberts et al. (2017) it was seen that nitrate increased GH in rats and humans, with nitric oxide being another candidate that may contribute to the increase of GH caused by exercise. The JAK2 and STAT5 proteins that participate in the GH signaling pathway are phosphorylated in response to acute exercise in the skeletal muscle, this suggests that the increase in GH after exercise can regulate this pathway in humans. It is important to investigate the physiological role of this pathway since most studies focus on the pathway related to IRS- PI3K-AKT and MAPK (Consitt et al., 2008).

Acute strenght exercise

The peak GH release in response to strength exercise occurs near the end of exercise and returns to baseline values 90 min post-exercise, this same pattern of secretion is seen in aerobic exercise (WJ Kraemer et al., 1993; William J Kraemer et al. (1999) and Nari et al. The interval time between the series, the load and the frequency of the protocol used in the strenght exercise influence the secretion of the GH, and as in aerobic exercises, the secretion is quite variable among the individuals (Raastad, Bjøro, and Hallén 2000). A review by Kraemer et al (1990) found that the protocols that are most effective in increasing GH secretion in men involve high total volume and short rest periods, or high repetitions with moderate potency (WJ Kraemer et al., 1990; Vanhelder, Radomski, and Goode 1984, Bosco et al., 2000). On the other hand, in women, the greatest GH responses are with long-term protocols and shorter rest periods, combined with moderately heavy resistance. Likewise, multiple series resulted in greater and more prolonged GH secretion than only one series (W J Kraemer et al., 1993). Interestingly Takarada et al. (2000) showed that GH increased significantly when vascular occlusion occurred simultaneously with strength exercise with an intensity of 20% of 1RM, the authors attributed this effect to the accumulation of local metabolites. In the study by Manini et al. (2012) where they compared the response of GH secretion to the exercise of high-intensity strength and low intensity with vascular occlusion, it was observed that in young men the exercise with low intensity and vascular occlusion resulted in the maximum response of GH that correlated with the lactate levels. Deemer et al. (2018) were the first to investigate the effect of high-intensity interval training on GH pulsatile secretion with measures even performed overnight, from one day to the next. The results showed that high- intensity interval training increased pulsatile secretion compared to control, but did not influence the nocturnal secretory pattern. In addition, this type of exercise increased the area under the curve measured an hour and a half after exercise.

Age influences the GH peak and the area under the integrated GH curve when these responses are analyzed after exercise in the elderly compared to younger people so that in the elderly these effects are lower (Marcell et al. G Pyka, Wiswell, and Marcus 1992). The difference between the age groups may be due to methodological differences, particularly due to the difficulty in equalizing the total work performed or the intensity of the exercise (Laurie Wideman et al., 2002b). Moreover, according to Wideman (2002), the studies that analyze the GH secretion response to acute strength exercise besides the difficulty in equalizing the intensity between the individuals and studies, have technical limitations because it is difficult to collect the blood without interfering in the progression of the exercise and the collections are usually before, sometimes in the interval between the exercises and at various times after exercise. However, pulsatile release in 24 hours is a parameter that should be analyzed when investigating the response of GH secretion after strenght exercise. For these reasons, Contrary

to aerobic exercises, studies examining the dynamics of GH secretion after exercise are scarce (Bradley C. Nindl et al., 2014). In the work of Nindl et al. (2014) were analyzed in young men for each type of acute, strength and aerobic exercise, two different durations, moderate (1h) and long (2h) in order to investigate the GH secretion pattern during the 20h following the recovery of exercise sessions. The results showed that only long-term aerobic exercise increased GH secretion (the pulses had greater amplitude, there was a higher rate of basal secretion, greater total basal secretion, greater total pulsatile secretion and greater total secretion as a whole). Surprisingly, this result was not observed in strength exercise sessions. The authors suggest that the increased energy expenditure provided by aerobic exercise with high demands for fat mobilization after exercise could explain this result. Surya et al. (2009) show that only pulsatile secretion of GH, not continuous, implies lipolytic effects in humans.

Interestingly, in men and young women, the average GH peak reached during aerobic exercise and strength is between 5-25μg / L (the peak in very intense aerobic exercise (90% VO2max) can reach 50μg / L) (Laurie Wideman et al., 2002b). Given that the magnitude of the GH secretion response depends on the intensity and the appropriate duration used in the exercise used, this is useful for all age groups, so that the intensity of the burden in the elderly should be relatively higher than in young individuals for achieving the same substantial increase in GH (A. Weltman et al 2000).

Aerobic training

Some studies show that when endurance-trained individuals undergo an acute exercise session with a constant load, the GH release is reduced when the absolute load is not modified (JA Kanaley et al., 1997; Hartley et al., 1972), suggesting that the relative load has greater influence than the absolute on the GH release induced by exercise.

In young women who participated in endurance training for 1 year, there was a significant increase in integrated GH concentration for 24 h when training was performed at an intensity above the lactate threshold (Weltman et al., 1992). Adults with metabolic syndrome increased nocturnal spontaneous GH secretion after 16 weeks of training, regardless of intensity (Irving et al., 2009). In the same way, comparing elite young athletes (very intense training, at least 12 hours a week) of various sport modalities, with non-elite athletes (moderate training from 3 to 9h / week) and sedentary subjects (less than 3h / week), GH presented higher levels in elite athletes, with no alterations between groups related to IGF-1, in this study there was a strong correlation between GH levels and training intensity (Ubertini et al. In young and middle-aged cyclists, 4- month progressive endurance training did not increase GH release in response to acute cycle ergometer exercise, although both groups increased maximal oxygen uptake. Middle-aged cyclists had a lower response to peak exercise and a lower baseline GH when compared to young subjects. However, one limitation of this study was that no comparison was made with the sedentary pairs in each group, and the spontaneous release of GH for 24 hours in response to the training was not measured (Zaccaria et al., 1999b). GH secretion is less responsive to aerobic training in the elderly, but more studies are needed to evaluate the training response in the elderly. In a study with elderly men (50-78 years), serum IGF-1 concentration does not differ between a group of marathoners and sedentary men of the same age (Deuschle et al., 1998). According to Wideman (2002), the lack of response may be due to a lack of sufficient stimulation, exercise not being able to reduce body fat, mainly visceral fat, both correlated with GH secretion in older adults and the intrinsic aging of the GH-IGF-1 axis.

Strength Training

The basal GH concentration does not change in response to strength training. One study evaluated baseline GH concentration in resting men for 24 hours after 10 weeks of strength training and found a reduction in mean GH concentration compared to the pre-training period, but the area under the curve was not measured at different times training.

Methodological limitations in the studies hinder the conclusion regarding the effect of strength training on GH secretion, for example, in the work of Marx et al. (2001) nor the periodized protocol strenght exercise with high volume, nor the training in circuit with low volume altered the basal levels of GH after 24 weeks of training, however only one collection was made before the beginning of the training, with 12 and with 24 weeks of training. On the other hand, significant increases were observed after 12-week strength training in GH concentration when young and old subjects underwent an acute strenght exercise session (Craig, Brown, and Everhart 1989). However, although elderly men increased GH concentration when undergoing a strenght exercise session, training for 12 weeks did not increase the acute exercise response on GH secretion (Craig, Brown, and Everhart 1989). Several other studies corroborate these data (William J Kraemer et al., 1999; K Häkkinen et al., 2000, Gisela Pyka, Taaffe, and Marcus 1994), even when the release of integrated GH for 24 hours in healthy elderly subjects (59- 79 years), aerobic training performed 4 days/week together with strength training performed 3 days/week did not change the integrated GH concentration for 24 hours (Arthur Weltman et al., 2000).

However, further studies are needed to understand how GH secretion in elderly post-effort works by analyzing this parameter. However, most of the data point to a decrease in GH secretion response in the elderly to strength training.

Many studies show increases in strength in the elderly without an increase in GH (K Häkkinen et al., 2000; Keijo Häkkinen et al., 2002; WJ Kraemer et al., 1998), suggesting that others factors such as neuromuscular adaptations may be important for this functional response. Again, the type of exercise and total work employed are important elements when designing a training program to induce GH secretion in response to strength training. However, it is important to exercise caution in prescribing as the magnitude of the load and intensity applied to achieve an effect in training may exceed the limits borne by the elderly and cause some type of injury.

GH and Exercise - Some considerations

GH secreted in response to exercise could contribute to the aerobic post- exercise anabolic effect in young and old (Short et al., 2004; Sheffield- Moore et al., 2004), either directly or indirectly through increased lipolysis. Studies using animals have shown that increased availability of fatty acids reduces leucine oxidation (Tessari et al., 1986) and in non-trained humans, fat oxidation showed a negative correlation with protein oxidation (Solini et al., 1997). These anabolic effects of GH related to its lipolytic effect were also confirmed by a study in which the effect of GH to conserve the protein during fasting was abolished by the administration of the anti-lipolytic agent acipimox (Nørrelund et al. The administration of acipimox has also been used to demonstrate that GH increases the triglyceride content in skeletal muscle through its effect on promoting insulin resistance (Krag et al., 2007). The importance of this is unclear since the increase in skeletal muscle triglyceride is observed, paradoxically, in both insulin-resistant individuals and resistance-trained athletes (Goodpaster et al., 2001). The rates of GH secretion for 24 hours and plasma IGF-1 levels correlate positively

with VO2max and time spent practicing physical activity (Eliakim et al., 1996), while training with long- term exercise doubles the integrated concentration in women on days without exercise (Weltman et al., 1992). Levels of total and free IGF-1 and IGFBP3 increase after training (Roelen et al., 1997) and increased levels of IGF-1 become detectable within 2 weeks of initiation of training (Roelen et al., 1997) , remaining above the basal concentration for at least 6 months (Koziris et al., 1999). These long-term effects of exercise on the GH-IGF1 axis may also contribute to some of the effects of training, including increased muscle mass and increased cardiac output, although there is no evidence for this currently.

Doping

Thirty-five years ago, the first publication that GH was cited as an abuse drug was in the Underground Steroid Book, written by Daniel Duchaine in 1982. In this book, Californian Daniel Duchaine, then considered the steroid guru, makes clear the widespread use by athletes and practitioners of physical activity and empirically reports some effects observed with the administration of GH, including recommendations on its use.

In 1987, a review of the effects of GH was published without data in adults still available (Salomon and Sonksen 1987), but in 1989 the role of GH in growth hormone deficient subjects began to be investigated, and two of these publications have become fundamental for the understanding of the importance of GH in adult life, since both evidenced the role of the hormone in the regulation of body composition, bone metabolism and substrates (Salomon et al., 1989; Jørgensen et al., 1989).

Studies in the elderly and published in the early 1990s showed that elderly patients who received doses of GH of 0.03 mg/kg for 6 months had an increase of 8.8% in lean body mass, a reduction of 14.4% of fat mass, 1.6% increase in bone mineral density in the lumbar spine, and skin thickness increased by 7.1%. The results show that GH reduction is partly responsible for the reduction of lean mass, increased adipose tissue and thinner skin, which are characteristics that accompany the aging process (Rudman et al., 1990). Improvement in these parameters after administration of GH in these subjects made GH a promising hormone in combating the undesirable characteristics related to the aging process and some doctors and health professionals used media advertisements and began to present it as an anti-aging formula and as a magic potion for youth. However, to date, it is not indicated for aesthetic or anti-aging purposes, due to some of its effects still lacking scientific evidence and safety-related issues. Until 1987, the only source of GH was cadaveric, that is, the extraction of GH was made from pituitary glands of human cadavers and was used for the treatment of people with disabilities. However, this form of treatment was withdrawn from circulation in 1985 because it is related to the occurrence of Creutzfeldt-Jakob disease (encephalopathy characterized by slowly progressive dementia). In 1987, thanks to genetic engineering technology using recombinant DNA bacterial techniques, the first version of recombinant human growth hormone (rhGH) became available, making it possible to replace previous treatment with fewer health risks (Saugy 2006 Sönksen and Holt 2009). In addition, due to the greater availability of rhGH from the new technique, the treatment that was previously intended only for children with GHD who presented short stature, was extended to children with short stature of all causes, besides also attending adults with GHD. Currently, in Brazil, rhGH treatment is approved for children and adults with GHD, Turner syndrome, children born small for gestational age (SGA), idiopathic short stature, chronic renal failure and Prader-Willi syndrome (Portes, Jorge, and Jr. 2008; Damiani 2008). Even the indications being restricted to these cases, the use of GH in the history of the sport is not something unusual. Some cases stand out as that of former Canadian sprinter

Ben Johson, who was considered the world's fastest man in the late 1980s. Ben Johnson was world champion in 1988 at the Summer Olympics in Seoul for only 48 hours, losing the gold medal and the record in the 100 meters. His test tested positive for stanozolol, an anabolic steroid, and he admitted to using a GH-containing cocktail of drugs (Richard I. G. Holt 2009). Canadian sprinter Angella Issanjenko has also admitted to using hGH along with other drugs (Holt 2009).

Eight years later, in 1996, the Atlanta Olympic Games became known to some athletes as "The GH Games" because of the wide popularity of hormone use among athletes (R. IG Holt, Erotokritou-Mulligan, and Sönksen 2009). Chinese swimmer Yuan was invited to leave the 1999 World Swimming Championships after finding 13 bottles of human GH in his belongings. Most recently, during a legal briefing, Tim Montgomery, a former record-breaking athlete who set the 100-meter mark, admitted receiving a steroid GH supplement for 8 weeks. In addition to the athletes, famous action film star Silvester Stallone in 2007 was apprehended by police when he arrived in Sydney, Australia, and later sued by the Australian court for illegal GH imports (McHugh et al., 2005; Saugy 2006). At the end of the year 2015, an Al Jazeera documentary said that NFL star Peyton Manning and four other football league athletes used rhGH. The investigation is still going on and the future of the player is open. In a report, Charlie Sly, a pharmacist from Austin, Texas, who worked for the Guyer Institute, an anti-aging clinic in 2011, told the alleged doping case. According to recordings made with a secret camera, he appears on video stating that he was part of the medical staff that helped Manning recover from surgery and sent lots of drugs to Ashley, like rhGH.

In 1989, the IOC placed GH on its list of banned drugs in the category of peptide hormones and analogs, but it was only in 2004 at the Olympic Games in Athens that a test was developed to detect GH abuse (R. IG Holt, Erotokritou -Mulligan, and Sönksen 2009). However, because the exogenous biosynthetic GH has the amino acid sequence identical to that which is secreted by the pituitary gland (GH-22K) and due to the pulsatile pattern of GH secretion, its detection becomes difficult, making it impossible to use tests to identify unknown substances and tests that accurately signal high levels of GH in the blood. Two major strategies for detecting GH in blood samples are currently used: the test that measures the different GH isoforms and the biomarkers test (Baumann 2012a; WADA, 2016). However, research continues to advance to identify new markers that indicate the use of GH in anti-doping tests (Tan et al., 2017). It should be noted here some adverse effects of excess GH. They are: increased fluid and sodium retention, which can lead to hypertension, edema, paresthesia, carpal tunnel syndrome, joint stiffness, soft tissue swelling; arthralgias; myalgias; insulin resistance; gynecomastia and acromegaly, which is a chronic disease caused by excess GH where there is an increase in the thickness of bones and soft parts of the body, especially the bones of the hands, feet and membranous bones (eg skull, nose, lower jaw, vertebrae). In addition, organs such as tongue, liver, and kidneys also increase (Baumann 2012b). Excess GH may cause cardiac hypertrophy (Colao 2008). Adverse effects are dose-dependent and treatment duration-dependent, age may also influence, elderly are more susceptible to adverse effects even using low doses (Baumann 2012b)

Is there scientific evidence to justify the use of GH to improve physical performance?

The use of GH by a range of athletes of several different styles shows that perhaps it may have some positive effect on physical performance in athletes and physical activity practitioners, but from the scientific point of view few studies show these improvements (Liu et al. ; UJ Meinhardt and Ho 2007).

Liu et al. (2008) performed a systematic review of the effects of GH on various parameters related to athletic performance, such as muscular strength and physical capacity measured through oxygen consumption. In this review, 27 studies were evaluated, with a total number of 440 participants (of whom 303 were treated with GH), these participants were classified as physically active and were aged between 13-45 years (mean age 27 years), subjects were lean, with a body mass index of 24 kg / m2. Seven studies administered GH only once and 20 studies administered GH for more than one day, in which the duration of the treatment had on average 20 days. Only three had more than 30 days in duration and none exceeded the duration of 3 months. The mean daily dose was 36 μg / kg for the 27 studies. Although short-term GH was able to increase lean body mass by promoting changes in body composition, no improvement in muscle strength or VO2max was detected in subjects treated with GH. The authors concluded that the increase in physical performance caused by GH is not scientifically supported, and further studies are needed in this area. However, some factors may have contributed to these effects, such as the duration of treatment and the daily dosage of GH used, it may be that a longer duration of administration and larger daily dosages are necessary to show positive effects in these parameters. In the study by Liu et al. the longest treatment period lasted 3 months, in addition, the daily average used by athletes is 15-180μg / kg (Saugy 2006), exceeding the dosage of the study by Liu et al. (2008).

Also in the 1990s, many studies were published showing the effect of rhGH on people with GH deficiency. In these studies, there was an increase in muscle mass and strength (Cuneo, Salomon, Wiles, Hesp, and Sonksen 1991) with increased isometric strength and long-term isokinetic effect after 2 years of rhGH treatment, and this increase was more marked in patients who had lower age-predicted strength (Johannsson et al., 1997). In 1992 and 1995, two papers were published, the first in young men and the second in elderly men, and neither showed an additional effect on hypertrophy and strength beyond those already promoted by the resistance exercise after GH administration for a period of 12 and 16 weeks, respectively (Yarasheski et al., 1992, 1995).

In 2005, a study that showed a 5-year remission in patients with hypopituitarism (Götherström et al., 2005) or in people with high catabolic status, such as HIV, showed that endurance capacity improved in these individuals. However, these results can not be compared to the status of athletes undergoing training (Cuneo, Salomon, Wiles, Hesp, and Sönksen 1991; Felbinger et al., 1999;

The effects of hormone replacement are more pronounced when hormone levels are at low levels (this is a basic principle in endocrinology), this may explain the effects observed in people with GHD and non-reproducibility in normal individuals. Athletes' abuse of both GH withdrawn from cadaver pituitaries and that developed in the 1980s through recombinant DNA technology shows that they believed that the effects observed in GHD could be extrapolated to healthy individuals (Graham et al., 2008).

Crist et al. (1988) and Deyssig et al. (1993) studied the effect of GH on athletes and had conflicting results after 6 weeks of replacement. The first one saw a significant difference in parameters related to body composition and the second did not, besides the latter also tested the strength of contraction of the biceps and quadriceps and did not see the difference.

Graham et al. (2008) were able to demonstrate many positive effects after only 6 days of administering a modest dose (0.058 IU.kg-1.dia-1) of rhGH in a group of former users of anabolic steroids (EAS). Part of the reason they were able to show so many positive effects was that the effect of GH can be amplified with the use of EAS so that the administration of Testosterone and GH increases the expression of the predominant androgenic and IGF-1 receptors in skeletal muscle. Therefore, it is possible that former users were sensitive to GH.

This effect had already been known for some time by coaches and athletes who used both hormones at the same time, as Duchaine's (1982) book tells us.

A group of Australian researchers showed effects on body composition and performance following administration of GH alone or after combined use of GH and testosterone. They found in those who used GH lower fat mass, increased fat-free mass through the increase of extracellular water, this also occurred with the combined treatment of testosterone. In addition, sprint capacity time increased in men and women by 3.9 and 8.3% respectively in the group that used only GH, this suggests a competitive advantage in sprint sports and justifies GH being a substance banned by the Agency World Anti-Doping Agency (WADA). In addition, the effects may be greater as the dose and administration time was lower than that used by athletes. However, more studies need to be done because this work was the first to demonstrate advantages of GH in sports performance (U. Meinhardt et al., 2010). GH and rhGH appear to stimulate IGF-1 class 1 isoform production locally in muscle and tendon. This may help prevent muscle and tendon rupture in EAA users who develop muscle hypertrophy. The strenght transmission from muscle fiber to bone could be explained by the effect of GH stimulation on collagen synthesis. The strength of the connective tissue promotes a more resistant muscle-tendon junction and may explain why there is a clamor for the effect of rhGH on increasing athletic performance despite the scientific literature contradicting such postulates (Doessing and Kjaer 2005; Berggren et al., 2005; Ehrnborg et al. 2005).

CONCLUSION

The scientific evidence shown in this review shows that GH, besides being an important modulator of energetic metabolism at rest, seems to have great importance during and after physical exercises of different types. In lipid metabolism, GH can have direct and indirect lipolytic effects, stimulating the mobilization of free fatty acids in the adipose tissue to generate energy, increasing sensitivity to catecholamines, or even decreasing the anti-lipolytic action of insulin. And although it serves to increase the lean mass of people who have low blood GH levels, such an anabolic effect on the skeletal muscles in normal people has not been proven. These GH effects essentially related to anabolic, lipolytic and antinatriuretic properties, besides their difficult detection in the blood, are one of the main reasons why athletes and practitioners of physical activity make use of this hormone. Although GH has been a banned substance in the sport since the late 1980s, both official and unofficial sources have reported increasing increases in GH abuse in sport.

However, based on the scientific evidence presented in this study, there is insufficient data in the literature to show an increase in physical performance to justify the abuse of GH by athletes and physical activity practitioners.

FUTURE RESEARCH

In addition, more studies are needed to continue unveiling the mechanisms that regulate GH secretion in response to exercise, it is important that training protocols are also stipulated that can stimulate its secretion in elderly and obese people to prevent or reduce the deleterious effects caused conditions.

Epidemiological studies are also important to support educational programs that enhance the knowledge of athletes, physical activity practitioners and professionals in the area regarding health risks when using GH for both performance and aesthetic purpose.

REFERENCES

Åberg, N. David, Katarina Gustafson Brywe, and Jörgen Isgaard. 2006. "Aspects of Growth Hormone and Insulin-Like Growth Factor-I Related to Neuroprotection, Regeneration, and Functional Plasticity in the Adult Brain." *The Scientific World JOURNAL* 6: 53–80. doi:10.1100/tsw.2006.22.

Amit, T, M B Youdim, and Z Hochberg. 2000. "Clinical Review 112: Does Serum Growth Hormone (GH) Binding Protein Reflect Human GH Receptor Function?" *The Journal of Clinical Endocrinology and Metabolism* 85 (3): 927–32. doi:10.1210/jcem.85.3.6461.

Ashmore, Tom, Lee D Roberts, Andrea J Morash, Aleksandra O Kotwica, John Finnerty, James A West, Steven A Murfitt, et al. 2015. "Nitrate Enhances Skeletal Muscle Fatty Acid Oxidation via a Nitric Oxide-cGMP-PPAR-Mediated Mechanism." *BMC Biology* 13 (1): 110. doi:10.1186/s12915-015-0221-6.

Auriemma, Renata S, Mariano Galdiero, Maria C De Martino, Monica De Leo, Ludovica F S Grasso, Pasquale Vitale, Alessia Cozzolino, Gaetano Lombardi, Annamaria Colao, and Rosario Pivonello. 2010. "The Kidney in Acromegaly: Renal Structure and Function in Patients with Acromegaly during Active Disease and 1 Year after Disease Remission." *European Journal of Endocrinology* 162 (6): 1035–42. doi:10.1530/EJE-10-0007.

Baumann, Gerhard, Klaus Amburn and Melissa A. Shawn. 1988. "The Circulating Growth Hormone (GH)-Binding Protein Complex: A Major Constituent of Plasma GH in Man*." *Endocrinology* 122 (3): 976–84. doi:10.1210/endo-122-3-976.

Baumann, Gerhard P. 2012a. "Growth Hormone Doping in Sports: A Critical Review of Use and Detection Strategies." *Endocrine Reviews* 33 (2): 155–86. doi:10.1210/er.2011-1035.

Baumann, Gerhard P. 2012b. "Growth Hormone Doping in Sports: A Critical Review of Use and Detection Strategies." *Endocrine Reviews* 33 (2): 155–86. doi:10.1210/er.2011-1035.

Berggren, Annika, Christer Ehrnborg, Thord Rosén, Lars Ellegård, Bengt-Åke Bengtsson, and Kenneth Caidahl. 2005. "Short-Term Administration of Supraphysiological Recombinant Human Growth Hormone (GH) Does Not Increase Maximum Endurance Exercise Capacity in Healthy, Active Young Men and Women with Normal GH-Insulin-Like Growth Factor I Axes." *The Journal of Clinical Endocrinology & Metabolism* 90 (6): 3268–73. doi:10.1210/jc.2004-1209.

Bosco, C, R Colli, R Bonomi, S P von Duvillard, and A Viru. 2000. "Monitoring Strength Training: Neuromuscular and Hormonal Profile." *Medicine and Science in Sports and Exercise* 32 (1): 202–8.

Brauman, H, and J Corvilain. n.d. "[Effect of Hypoglycemia on Secretion of Somatotropic Hormone (STH) in Myxedema]." *Annales D'endocrinologie* 29 (4): 465–72.

Brillon, D, N Nabil, and L S Jacobs. 1986. "Cholinergic but Not Serotonergic Mediation of Exercise-Induced Growth Hormone Secretion." *Endocrine Research* 12 (2): 137–46.

Brooks, Andrew J, and Michael J Waters. 2010. "The Growth Hormone Receptor: Mechanism of Activation and Clinical Implications." *Nature Reviews. Endocrinology* 6 (9): 515–25. doi:10.1038/nrendo.2010.123.

Burman, Pia, Anna G. Johansson, Agneta Siegbahn, Bengt Vessby, and F. Anders Karlsson. 1997. "GH)-Deficient Men Are More Responsive to GH Replacement Therapy than Women." *J Clin Endocrinol Metab* 82 (2): 550–55.

Callewaert, Filip, Mieke Sinnesael, Evelien Gielen, Steven Boonen, and Dirk Vanderschueren. 2010. "Skeletal Sexual Dimorphism: Relative Contribution of Sex Steroids, GH-IGF1, and Mechanical Loading." *The Journal of Endocrinology* 207 (2): 127–34. doi:10.1677/JOE-10-0209.

Cermak, Naomi M, Martin J Gibala, and Luc J C van Loon. 2012. "Nitrate Supplementation's Improvement of 10-Km Time-Trial Performance in Trained Cyclists." *International Journal of Sport Nutrition and Exercise Metabolism* 22 (1): 64–71.

Chang, F E, W G Dodds, M Sullivan, M H Kim, and W B Malarkey. 1986. "The Acute Effects of Exercise on Prolactin and Growth Hormone Secretion: Comparison between Sedentary Women and Women Runners with Normal and Abnormal Menstrual Cycles." *The Journal of Clinical Endocrinology and Metabolism* 62 (3): 551–56. doi:10.1210/jcem-62-3-551.

Christensen, S E, O L Jørgensen, N Møller, and H Orskov. 1984. "Characterization of Growth Hormone Release in Response to External Heating. Comparison to Exercise Induced Release." *Acta Endocrinologica* 107 (3): 295–301.

Clark, R G, D L Mortensen, L M Carlsson, S A Spencer, P McKay, M Mulkerrin, J Moore, and B C Cunningham. 1996. "Recombinant Human Growth Hormone (GH)-Binding Protein Enhances the Growth-Promoting Activity of Human GH in the Rat." *Endocrinology* 137 (10): 4308–15. doi:10.1210/endo.137.10.8828490.

Coiro, V, L E Braverman, D Christianson, S L Fang, and H M Goodman. 1979. "Effect of Hypothyroidism and Thyroxine Replacement on Growth Hormone in the Rat." *Endocrinology* 105 (3): 641–46. doi:10.1210/endo-105-3-641.

Colao, Annamaria. 2008. "The GH-IGF-I Axis and the Cardiovascular System: Clinical Implications." *Clinical Endocrinology* 69 (3): 347–58. doi:10.1111/j.1365-2265.2008.03292.x.

Consitt, Leslie A, Laurie Wideman, Matthew S Hickey, and Ron F Morrison. 2008. "Phosphorylation of the JAK2-STAT5 Pathway in Response to Acute Aerobic Exercise." *Medicine and Science in Sports and Exercise* 40 (6): 1031–38. doi:10.1249/MSS.0b013e3181690760.

Craig, B W, R Brown, and J Everhart. 1989. "Effects of Progressive Resistance Training on Growth Hormone and Testosterone Levels in Young and Elderly Subjects." *Mechanisms of Ageing and Development* 49 (2): 159–69.

Crist, D M, G T Peake, P A Egan, and D L Waters. 1988. "Body Composition Response to Exogenous GH during Training in Highly Conditioned Adults." *Journal of Applied Physiology (Bethesda, Md. : 1985)* 65 (2): 579–84. doi:10.1152/jappl.1988.65.2.579.

Cuneo, R. C., F. Salomon, C. M. Wiles, R. Hesp, and P. H. Sonksen. 1991. "Growth Hormone Treatment in Growth Hormone-Deficient Adults. I. Effects on Muscle Mass and Strength." *Journal of Applied Physiology* 70 (2): 688–94. doi:10.1152/jappl.1991.70.2.688.

Cuneo, R C, F Salomon, C M Wiles, R Hesp, and P H Sönksen. 1991. "Growth Hormone Treatment in Growth Hormone-Deficient Adults. I. Effects on Muscle Mass and Strength." *Journal of Applied Physiology (Bethesda, Md. : 1985)* 70 (2): 688–94.

Damiani, Durval. 2008. "[Growth Hormone Usage in Prader-Willi Syndrome]." *Arquivos Brasileiros de Endocrinologia E Metabologia* 52 (5): 833–38.

Deemer, Sarah E, Todd J Castleberry, Chris Irvine, Daniel E Newmire, Michael Oldham, George A King, Vic Ben-Ezra, Brian A Irving, and Kyle D Biggerstaff. 2018. "Pilot Study: An Acute Bout of High Intensity Interval Exercise Increases 12.5 H GH Secretion." *Physiological Reports* 6 (2): e13563. doi:10.14814/phy2.13563.

DENKO, C W, and D M BERGENSTAL. 1955. "The Effect of Hypophysectomy and Growth Hormone on S35 Fixation in Cartilage." *Endocrinology* 57 (1): 76–86. doi:10.1210/endo-57-1-76.

Deuschle, M, W F Blum, J Frystyk, H Orskov, U Schweiger, B Weber, A Körner, et al. 1998. "Endurance Training and Its Effect upon the Activity of the GH-IGFs System in the Elderly." *International Journal of Sports Medicine* 19 (4): 250–54. doi:10.1055/s-2007-971913.

Deyssig, R, H Frisch, W F Blum, and T Waldhör. 1993. "Effect of Growth Hormone Treatment on Hormonal Parameters, Body Composition and Strength in Athletes." *Acta Endocrinologica* 128 (4): 313–18.

Doessing, S., and M. Kjaer. 2005. "Growth Hormone and Connective Tissue in Exercise." *Scandinavian Journal of Medicine and Science in Sports* 15 (4): 202–10. doi:10.1111/j.1600-0838.2005.00455.x.

Duchaine, D. 1982. *Underground Steroid Handbook. HLR Technical Books*. Venice, California, USA.

Ehrnborg, Christer, Lars Ellegard, Ingvar Bosaeus, Bengt-Ake Bengtsson, and Thord Rosen. 2005. "Supraphysiological Growth Hormone: Less Fat, More Extracellular Fluid but Uncertain Effects on Muscles in Healthy, Active Young Adults." *Clinical Endocrinology* 62 (4): 449–57. doi:10.1111/j.1365-2265.2005.02240.x.

Eliakim, A, J A Brasel, S Mohan, T J Barstow, N Berman, and D M Cooper. 1996. "Physical Fitness, Endurance Training, and the Growth Hormone-Insulin-like Growth Factor I System in Adolescent Females." *The Journal of Clinical Endocrinology and Metabolism* 81 (11): 3986–92.

doi:10.1210/jcem.81.11.8923848.

Elias, A N, A F Wilson, S Naqvi, and M R Pandian. 1997. “Effects of Blood pH and Blood Lactate on Growth Hormone, Prolactin, and Gonadotropin Release after Acute Exercise in Male Volunteers.” *Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine (New York, N.Y.)* 214 (2): 156–60.

Esposito, Andrea, Donatella Capalbo, Lucia De Martino, Martina Rezzuto, Raffaella Di Mase, Claudio Pignata, and Mariacarolina Salerno. 2016. “Long-Term Effects of Growth Hormone (GH) Replacement Therapy on Hematopoiesis in a Large Cohort of Children with GH Deficiency.” *Endocrine* 53 (1): 192–98. doi:10.1007/s12020-015-0781-9.

Esposito, John G., Scott G. Thomas, Lori Kingdon, and Shereen Ezzat. 2005. “Anabolic Growth Hormone Action Improves Submaximal Measures of Physical Performance in Patients with HIV-Associated Wasting.” *American Journal of Physiology-Endocrinology and Metabolism* 289 (3): E494–503. doi:10.1152/ajpendo.00013.2005.

Ewton, D Z, and J R Florini. 1981. “Effects of the Somatomedins and Insulin on Myoblast Differentiation in Vitro.” *Developmental Biology* 86 (1): 31–39.

Fanciulli, Giuseppe, Alessandro Delitala, and Giuseppe Delitala. 2009. “Growth Hormone, Menopause and Ageing: No Definite Evidence for ‘Rejuvenation’ with Growth Hormone.” *Human Reproduction Update* 15 (3): 341–58. doi:10.1093/humupd/dmp005.

Farhy, Leon S, Cyril Y Bowers, and Johannes D Veldhuis. 2007. “Model-Projected Mechanistic Bases for Sex Differences in Growth Hormone Regulation in Humans.” *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* 292 (4): R1577-93. doi:10.1152/ajpregu.00584.2006.

Felbinger, T W, U Suchner, A E Goetz, J Briegel, and K Peter. 1999. “Recombinant Human Growth Hormone for Reconditioning of Respiratory Muscle after Lung Volume Reduction Surgery.” *Critical Care Medicine* 27 (8): 1634–38.

Felsing, Nancy E., J O Anne, M Cooper, and West Carson Street. 1992. “Effect of Low and High Intensity Growth Hormone.” *JCEM* 75 (1): 157–62.

Ferrini, F, C Salio, L Lossi, and A Merighi. 2009. “Ghrelin in Central Neurons.” *Current Neuropharmacology* 7 (1): 37–49. doi:10.2174/157015909787602779.

FLORINI, JAMES R., DAINA Z. EWTON, and SHARON A. COOLICAN. 1996. “Growth Hormone and the Insulin-Like Growth Factor System in Myogenesis*.” *Endocrine Reviews* 17 (5): 481–517. doi:10.1210/edrv-17-5-481.

Freda, Pamela U., Wei Shen, Steven B. Heymsfield, Carlos M. Reyes-Vidal, Eliza B. Geer, Jeffrey N. Bruce, and Dympna Gallagher. 2008. “Lower Visceral and Subcutaneous but Higher Intermuscular Adipose Tissue Depots in Patients with Growth Hormone and Insulin-Like Growth Factor I Excess Due to Acromegaly.” *The Journal of Clinical Endocrinology & Metabolism* 93 (6): 2334–43. doi:10.1210/jc.2007-2780.

Galy, Olivier, Karim Chamari, Christelle Peyreigne, Jacques Mercier, and Olivier Hue. 2014. “Sequential Exercise in Triathletes: Variations in GH and Water Loss.” Edited by Alejandro Lucia. *PloS One* 9 (4): e96145. doi:10.1371/journal.pone.0096145.

Ghigo, E., J. Bellone, E. Arvat, E. Mazza, S. G. Cellat, F. Brambilla, E. E. Müller, and F. Camanni. 1990. “Effects of Alpha- and Beta-Adrenergic Agonists and Antagonists on Growth Hormone Secretion in Man.” *Journal of Neuroendocrinology* 2 (4): 473–76. doi:10.1111/j.1365-2826.1990.tb00435.x.

Giannoulis, Manthos G., Peter H. Sonksen, Margot Umpleby, Louise Breen, Claire Pentecost, Martin Whyte, Carolyn V. McMillan, Clare Bradley, and Finbarr C. Martin. 2006. “The Effects of Growth Hormone And/or Testosterone in Healthy Elderly Men: A Randomized Controlled Trial.” *The Journal of Clinical Endocrinology & Metabolism* 91 (2): 477–84. doi:10.1210/jc.2005-0957.

Giustina, a, and J D Veldhuis. 1998. “Pathophysiology of the Neuroregulation of Growth Hormone Secretion in Experimental Animals and the Human.” *Endocrine Reviews* 19 (6): 717–97. doi:10.1210/edrv.19.6.0353.

Giustina, Andrea, Gherardo Mazziotti, and Ernesto Canalis. 2008. “Growth Hormone, Insulin-Like

Growth Factors, and the Skeleton." *Endocrine Reviews* 29 (5): 535–59. doi:10.1210/er.2007-0036.

Golde, D W, N Bersch, and C H Li. 1977. "Growth Hormone: Species-Specific Stimulation of Erythropoiesis in Vitro." *Science (New York, N.Y.)* 196 (4294): 1112–13.

Goldenberg, Naila, and Ariel Barkan. 2007. "Factors Regulating Growth Hormone Secretion in Humans." *Endocrinology and Metabolism Clinics of North America* 36 (1): 37–55. doi:10.1016/j.ecl.2006.11.003.

Goodpaster, Bret H., Jing He, Simon Watkins, and David E. Kelley. 2001. "Skeletal Muscle Lipid Content and Insulin Resistance: Evidence for a Paradox in Endurance-Trained Athletes." *The Journal of Clinical Endocrinology & Metabolism* 86 (12): 5755–61. doi:10.1210/jcem.86.12.8075.

Götherström, Galina, Bengt-Ake Bengtsson, Katharina Stibrant Sunnerhagen, Gudmundur Johannsson, and Johan Svensson. 2005. "The Effects of Five-Year Growth Hormone Replacement Therapy on Muscle Strength in Elderly Hypopituitary Patients." *Clinical Endocrinology* 62 (1): 105–13. doi:10.1111/j.1365-2265.2004.02181.x.

Graham, Michael R., Peter Evans, Bruce Davies, and Julien S. Baker. 2008. "AAS, Growth Hormone, and Insulin Abuse: Psychological and Neuroendocrine Effects." *Therapeutics and Clinical Risk Management* 4 (3): 587–97.

Green, H, M Morikawa, and T Nixon. 1985. "A Dual Effector Theory of Growth-Hormone Action." *Differentiation; Research in Biological Diversity* 29 (3): 195–98.

Häkkinen, K, A Pakarinen, W J Kraemer, R U Newton, and M Alen. 2000. "Basal Concentrations and Acute Responses of Serum Hormones and Strength Development during Heavy Resistance Training in Middle-Aged and Elderly Men and Women." *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 55 (2): B95-105.

Häkkinen, Keijo, William J Kraemer, Arto Pakarinen, Travis Triplett-McBride, Jeffrey M McBride, Arja Häkkinen, Markku Alen, Michael R McGuigan, Roger Bronks, and Robert U Newton. 2002. "Effects of Heavy Resistance/power Training on Maximal Strength, Muscle Morphology, and Hormonal Response Patterns in 60-75-Year-Old Men and Women." *Canadian Journal of Applied Physiology = Revue Canadienne de Physiologie Appliquee* 27 (3): 213–31.

Hamarneh, Sulaiman R., Caitlin A. Murphy, Cynthia W. Shih, Walter Frontera, Martin Torriani, Javier E. Irazoqui, and Hideo Makimura. 2015. "Relationship Between Serum IGF-1 and Skeletal Muscle IGF-1 mRNA Expression to Phosphocreatine Recovery After Exercise in Obese Men With Reduced GH." *The Journal of Clinical Endocrinology & Metabolism* 100 (2): 617–25. doi:10.1210/jc.2014-2711.

Hansen, L H, X Wang, J J Kopchick, P Bouchelouche, J H Nielsen, E D Galsgaard, and N Billestrup. 1996. "Identification of Tyrosine Residues in the Intracellular Domain of the Growth Hormone Receptor Required for Transcriptional Signaling and Stat5 Activation." *The Journal of Biological Chemistry* 271 (21): 12669–73.

Hartley, L H, J W Mason, R P Hogan, L G Jones, T A Kotchen, E H Mougey, F E Wherry, L L Pennington, and P T Ricketts. 1972. "Multiple Hormonal Responses to Prolonged Exercise in Relation to Physical Training." *Journal of Applied Physiology* 33 (5): 607–10. doi:10.1152/jappl.1972.33.5.607.

Hartman, M L, A C Faria, M L Vance, M L Johnson, M O Thorner, and J D Veldhuis. 1991. "Temporal Structure of in Vivo Growth Hormone Secretory Events in Humans." *The American Journal of Physiology* 260 (1 Pt 1): E101-10.

Herrington, J, and C Carter-Su. 2001. "Signaling Pathways Activated by the Growth Hormone Receptor." *Trends in Endocrinology and Metabolism: TEM* 12 (6): 252–57.

Ho, K. Y., W. S. Evans, R. M. Blizzard, J. D. Veldhuis, G. R. Merriam, E. Samojlik, R. Furlanetto, A. D. Rogol, D. L. Kaiser, and M. O. Thorner. 1987. "Effects of Sex and Age on the 24-Hour Profile of Growth Hormone Secretion in Man: Importance of Endogenous Estradiol Concentrations." *Journal of Clinical Endocrinology and Metabolism* 64 (1): 51–58. doi:10.1210/jcem-64-1-51.

Ho, K K, A J O'Sullivan, and D M Hoffman. 1996. "Metabolic Actions of Growth Hormone in Man."

Endocrine Journal 43 Suppl (October): S57-63.

Holt, R. I G, Ioulietta Erotokritou-Mulligan, and Peter H. Sönksen. 2009. "The History of Doping and Growth Hormone Abuse in Sport." *Growth Hormone and IGF Research* 19 (4). Elsevier Ltd: 320–26. doi:10.1016/j.ghir.2009.04.009.

Holt, R. I G, E. Webb, C. Pentecost, and P. H. Sönksen. 2001. "Aging and Physical Fitness Are More Important than Obesity in Determining Exercise-Induced Generation of GH." *Journal of Clinical Endocrinology and Metabolism* 86 (12): 5715–20. doi:10.1210/jc.86.12.5715.

Holt, Richard I. G. 2009. "Detecting Growth Hormone Abuse in Athletes." *Drug Testing and Analysis* 1 (9â□'10): 426–33. doi:10.1002/dta.59.

Ignacio, DL, Diego H. Diego, João Paulo Albuquerque Cavalcanti-de-Albuquerque, Ruy Andrade Louzada, Denise P. Carvalho, and João Pedro Werneck-de-Castro. 2015. "Thyroid Hormone and Estrogen Regulate Exercise-Induced Growth Hormone Release." *PLoS ONE* 10 (4): 1–12. doi:10.1371/journal.pone.0122556.

Irving, Brian A., J. Y. Weltman, James T. Patrie, Christopher K. Davis, David W. Brock, Damon Swift, Eugene J. Barrett, Glenn A. Gaesser, and Arthur Weltman. 2009. "Effects of Exercise Training Intensity on Nocturnal Growth Hormone Secretion in Obese Adults with the Metabolic Syndrome." *Journal of Clinical Endocrinology and Metabolism* 94 (6): 1979–86. doi:10.1210/jc.2008-2256.

Jaffe, C a, B Ocampo-Lim, W Guo, K Krueger, I Sugahara, R DeMott-Friberg, M Bermann, and a L Barkan. 1998. "Regulatory Mechanisms of Growth Hormone Secretion Are Sexually Dimorphic." *The Journal of Clinical Investigation* 102 (1): 153–64. doi:10.1172/JCI2908.

Johannsson, Gudmundur, Gunnar Grimby, Katharina Stibrant Sunnerhagen, and Bengt-Åke Bengtsson. 1997. "Two Years of Growth Hormone (GH) Treatment Increase Isometric and Isokinetic Muscle Strength in GH-Deficient Adults [1]." *The Journal of Clinical Endocrinology & Metabolism* 82 (9). Oxford University Press: 2877–84. doi:10.1210/jcem.82.9.4204.

Jørgensen, J O, S A Pedersen, L Thuesen, J Jørgensen, T Ingemann-Hansen, N E Skakkebaek, and J S Christiansen. 1989. "Beneficial Effects of Growth Hormone Treatment in GH-Deficient Adults." *Lancet (London, England)* 1 (8649): 1221–25.

Kanaley, J. A., J. Y. Weltman, J. D. Veldhuis, A. D. Rogol, M. L. Hartman, and A. Weltman. 1997. "Human Growth Hormone Response to Repeated Bouts of Aerobic Exercise." *Journal of Applied Physiology* 83 (5): 1756–61. doi:10.1152/jappl.1997.83.5.1756.

Kanaley, J a, M M Weatherup-Dentes, E B Jaynes, and M L Hartman. 1999. "Obesity Attenuates the Growth Hormone Response to Exercise." *The Journal of Clinical Endocrinology and Metabolism* 84 (9): 3156–61. doi:10.1210/jcem.84.9.5997.

Katz, H P, R Youlton, S L Kaplan, and M M Grumbach. 1969. "Growth and Growth Hormone. 3. Growth Hormone Release in Children with Primary Hypothyroidism and Thyrotoxicosis." *The Journal of Clinical Endocrinology and Metabolism* 29 (3): 346–51. doi:10.1210/jcem-29-3-346.

Koziris, L P, R C Hickson, R T Chatterton, R T Groseth, J M Christie, D G Goldflies, and T G Unterman. 1999. "Serum Levels of Total and Free IGF-I and IGFBP-3 Are Increased and Maintained in Long-Term Training." *Journal of Applied Physiology (Bethesda, Md. : 1985)* 86 (4): 1436–42. doi:10.1152/jappl.1999.86.4.1436.

Kraemer, W J, S J Fleck, J E Dziados, E A Harman, L J Marchitelli, S E Gordon, R Mello, P N Frykman, L P Koziris, and N T Triplett. 1993. "Changes in Hormonal Concentrations after Different Heavy-Resistance Exercise Protocols in Women." *Journal of Applied Physiology (Bethesda, Md. : 1985)* 75 (2): 594–604.

Kraemer, W J, L Marchitelli, S E Gordon, E Harman, J E Dziados, R Mello, P Frykman, D McCurry, and S J Fleck. 1990. "Hormonal and Growth Factor Responses to Heavy Resistance Exercise Protocols." *Journal of Applied Physiology (Bethesda, Md. : 1985)* 69 (4): 1442–50.

Kraemer, W J, R S Staron, F C Hagerman, R S Hikida, A C Fry, S E Gordon, B C Nindl, et al. 1998. "The Effects of Short-Term Resistance Training on Endocrine Function in Men and Women." *European Journal of Applied Physiology and Occupational Physiology* 78 (1): 69–76. doi:10.1007/s004210050389.

Kraemer, William J, Keijo Häkkinen, Robert U Newton, Bradley C Nindl, Jeff S Volek, Matthew McCormick, Lincoln A Gotshalk, et al. 1999. "Effects of Heavy-Resistance Training on Hormonal Response Patterns in Younger vs. Older Men." *Journal of Applied Physiology* 87 (3): 982–92.

Krag, Morten B., Lars C. Gormsen, ZengKui Guo, Jens S. Christiansen, Michael D. Jensen, Søren Nielsen, and Jens O. L. Jørgensen. 2007. "Growth Hormone-Induced Insulin Resistance Is Associated with Increased Intramyocellular Triglyceride Content but Unaltered VLDL-Triglyceride Kinetics." *American Journal of Physiology-Endocrinology and Metabolism* 292 (3): E920–27. doi:10.1152/ajpendo.00374.2006.

Kreitschmann-Andermahr, Ilonka, Pablo Suarez, Rachel Jennings, Nina Evers, and Georg Brabant. 2010. "GH/IGF-I Regulation in Obesity--Mechanisms and Practical Consequences in Children and Adults." *Hormone Research in Pædiatrics* 73 (3): 153–60. doi:10.1159/000284355.

Kurtz, A, J Zapf, K U Eckardt, G Clemons, E R Froesch, and C Bauer. 1988. "Insulin-like Growth Factor I Stimulates Erythropoiesis in Hypophysectomized Rats." *Proceedings of the National Academy of Sciences of the United States of America* 85 (20): 7825–29.

Lanning, Nathan J., and Christin Carter-Su. 2007. "Recent Advances in Growth Hormone Signaling." *Reviews in Endocrine and Metabolic Disorders* 7 (4): 225–35. doi:10.1007/s11154-007-9025-5.

Lassarre, C, F Girard, J Durand, and J Raynaud. 1974. "Kinetics of Human Growth Hormone during Submaximal Exercise." *Journal of Applied Physiology* 37 (6): 826–30.

Leung, K C, N Doyle, M Ballesteros, K Sjogren, C K W Watts, T H Low, G M Leong, R J M Ross, and K K Y Ho. 2003. "Estrogen Inhibits GH Signaling by Suppressing GH-Induced JAK2 Phosphorylation, an Effect Mediated by SOCS-2." *Proceedings of the National Academy of Sciences of the United States of America* 100 (3): 1016–21. doi:10.1073/pnas.0337600100.

Liu, Hau, Dena M. Bravata, Ingram Olkin, Smita Nayak, Brian Roberts, Alan M. Garber, and Andrew R. Hoffman. 2007. "Systematic Review: The Safety and Efficacy of Growth Hormone in the Healthy Elderly." *Annals of Internal Medicine* 146 (2): 104–15. doi:10.7326/0003-4819-146-2-200701160-00005.

Liu, Hau, Dena M Bravata, Ingram Olkin, Anne Friedlander, Vincent Liu, Brian Roberts, Eran Bendavid, et al. 2008. "Review Systematic Review : The Effects of Growth Hormone on Athletic Performance." *Annals of Internal Medicine* 148 (10): 747–58. doi:148:747-758.

Lundberg, Jon O., Mattias Carlström, Filip J. Larsen, and Eddie Weitzberg. 2011. "Roles of Dietary Inorganic Nitrate in Cardiovascular Health and Disease." *Cardiovascular Research* 89 (3): 525–32. doi:10.1093/cvr/cvq325.

Manini, Todd M, Joshua F Yarrow, Thomas W Buford, Brian C Clark, Christine F Conover, and Stephen E Borst. 2012. "Growth Hormone Responses to Acute Resistance Exercise with Vascular Restriction in Young and Old Men." *Growth Hormone & IGF Research : Official Journal of the Growth Hormone Research Society and the International IGF Research Society* 22 (5): 167–72. doi:10.1016/j.ghir.2012.05.002.

Marcell, T J, R A Wiswell, S A Hawkins, and K M Tarpenning. 1999. "Age-Related Blunting of Growth Hormone Secretion during Exercise May Not Be Soley due to Increased Somatostatin Tone." *Metabolism: Clinical and Experimental* 48 (5): 665–70.

Marx, J O, N A Ratamess, B C Nindl, L A Gotshalk, J S Volek, K Dohi, J A Bush, et al. 2001. "Low-Volume Circuit versus High-Volume Periodized Resistance Training in Women." *Medicine and Science in Sports and Exercise* 33 (4): 635–43.

Mauras, Nelly, and Morey W Haymond. 2005. "Are the Metabolic Effects of GH and IGF-I Separable?" *Growth Hormone & IGF Research : Official Journal of the Growth Hormone Research Society and the International IGF Research Society* 15 (1): 19–27. doi:10.1016/j.ghir.2004.12.003.

McHugh, Cathy M., Roderick T. Park, Peter H. Sönksen, and R. I G Holt. 2005. "Challenges in Detecting the Abuse of Growth Hormone in Sport." *Clinical Chemistry* 51 (9): 1587–93. doi:10.1373/clinchem.2005.047845.

Meinhardt, Udo J, and Ken K Y Ho. 2007. "Regulation of Growth Hormone Action by Gonadal Steroids" 36 (2007): 57–73. doi:10.1016/j.ecl.2006.11.009.

Meinhardt, Udo, Anne E Nelson, Jennifer L Hansen, Vita Birzniece, David Clifford, Kin-Chuen Leung, Kenneth Graham, and Ken K Y Ho. 2010. "The Effects of Growth Hormone on Body Composition and Physical Performance in Recreational Athletes." *Annals of Internal Medicine* 152 (9): 568. doi:10.7326/0003-4819-152-9-201005040-00007.

Miki, N, M Ono, and K Shizume. 1984. "Evidence That Opiatergic and Alpha-Adrenergic Mechanisms Stimulate Rat Growth Hormone Release via Growth Hormone-Releasing Factor (GRF)." *Endocrinology* 114 (5): 1950–52. doi:10.1210/endo-114-5-1950.

Monson, John P, Antonia M Brooke, and Scott Akker. 2000. *Adult Growth Hormone Deficiency*. *Endotext*.

Müller, E E, V Locatelli, and D Cocchi. 1999. "Neuroendocrine Control of Growth Hormone Secretion." *Physiological Reviews* 79 (2): 511–607. doi:10.1152/physrev.1999.79.2.511.

Muller, Eugenio E., Vittorio Locatelli, and Daniela Cocchi. 1999. "Neuroendocrine Control of Growth Hormone Secretion." *Physiol Rev* 79 (2): 511–607.

Mulligan, Susan E, Steven J Fleck, Scott E. Gordon, L. Perry Koziris, N. Travis Triplett-McBride, and William J Kraemer. 1996. "Influence of Resistance Exercise Volume on Serum Growth Hormone and Cortisol Concentrations in Women." *The Journal of Strength and Conditioning Research* 10 (4): 256. doi:10.1519/1533-4287(1996)010<0256:IOREVO>2.3.CO;2.

Nindl, B C, W C Hymer, D R Deaver, and W J Kraemer. 2001. "Growth Hormone Pulsatility Profile Characteristics Following Acute Heavy Resistance Exercise." *Journal of Applied Physiology (Bethesda, Md. : 1985)* 91 (1): 163–72.

Nindl, Bradley C., Joseph R. Pierce, Kevin R. Rarick, Alexander P. Tuckow, Joseph A. Alemany, Marilyn A. Sharp, Mark D. Kellogg, and John F. Patton. 2014. "Twenty-Hour Growth Hormone Secretory Profiles after Aerobic and Resistance Exercise." *Medicine and Science in Sports and Exercise* 46 (10): 1917–27. doi:10.1249/MSS.0000000000000315.

Nørrelund, Helene, K Sreekumaran Nair, Steen Nielsen, Jan Frystyk, Per Ivarsen, Jens Otto Lunde Jørgensen, Jens Sandahl Christiansen, and Niels Møller. 2003. "The Decisive Role of Free Fatty Acids for Protein Conservation during Fasting in Humans with and without Growth Hormone." *The Journal of Clinical Endocrinology and Metabolism* 88 (9): 4371–78. doi:10.1210/jc.2003-030267.

Oliver, Stacy R, Jaime S Rosa, Timothy D C Minh, Andria M Pontello, Rebecca L Flores, Marcia Barnett, and Pietro R Galassetti. 2010. "Dose-Dependent Relationship between Severity of Pediatric Obesity and Blunting of the Growth Hormone Response to Exercise." *Journal of Applied Physiology (Bethesda, Md. : 1985)* 108 (1): 21–27. doi:10.1152/japplphysiol.00589.2009.

Pincus, S M, E F Gevers, I C Robinson, G van den Berg, F Roelfsema, M L Hartman, and J D Veldhuis. 1996. "Females Secrete Growth Hormone with More Process Irregularity than Males in Both Humans and Rats." *The American Journal of Physiology* 270 (1 Pt 1): E107-15.

Portes, Evandro S., Alexander Augusto de L. Jorge, and Carlos Eduardo Martinelli Jr. 2008. "Tratamento Com Hormônio de Crescimento – Aspectos Moleculares, Clínicos E Terapêuticos." *Abem* 52 (5): 715–16. doi:10.1590/S0004-27302008000500001.

Pritzlaff-Roy, Cathy J, Laurie Wideman, Judy Y Weltman, Rob Abbott, Margaret Gutgesell, Mark L Hartman, Johannes D Veldhuis, and Arthur Weltman. 2002. "Gender Governs the Relationship between Exercise Intensity and Growth Hormone Release in Young Adults." *Journal of Applied Physiology (Bethesda, Md. : 1985)* 92 (5): 2053–60. doi:10.1152/japplphysiol.01018.2001.

Pritzlaff, C J, L Wideman, J Y Weltman, R D Abbott, M E Gutgesell, M L Hartman, J D Veldhuis, and a Weltman. 1999. "Impact of Acute Exercise Intensity on Pulsatile Growth Hormone Release in Men." *Journal of Applied Physiology (Bethesda, Md. : 1985)* 87 (2): 498–504.

Pyka, G, R A Wiswell, and R Marcus. 1992. "Age-Dependent Effect of Resistance Exercise on Growth Hormone Secretion in People." *The Journal of Clinical Endocrinology and Metabolism* 75 (2): 404–7. doi:10.1210/jcem.75.2.1639942.

Pyka, Gisela, D. Taaffe, and R. Marcus. 1994. "Effect of a Sustained Program of Resistance Training on the Acute Growth Hormone Response to Resistance Exercise in Older Adults." *Hormone and Metabolic Research* 26 (7): 330–33. doi:10.1055/s-2007-1001697.

Raastad, T, T Bjøro, and J Hallén. 2000. “Hormonal Responses to High- and Moderate-Intensity Strength Exercise.” *European Journal of Applied Physiology* 82 (1–2): 121–28. doi:10.1007/s004210050661.

Redman, Leanne M, Johannes D Veldhuis, Jennifer Rood, Steven R Smith, Donald Williamson, Eric Ravussin, and Pennington CALERIE Team. 2010. “The Effect of Caloric Restriction Interventions on Growth Hormone Secretion in Nonobese Men and Women.” *Aging Cell* 9 (1): 32–39. doi:10.1111/j.1474-9726.2009.00530.x.

Roberts, Lee D., Tom Ashmore, Ben D. McNally, Steven A. Murfitt, Bernadette O. Fernandez, Martin Feelisch, Ross Lindsay, et al. 2017. “Inorganic Nitrate Mimics Exercise-Stimulated Muscular Fiber-Type Switching and Myokine and γ-Aminobutyric Acid Release.” *Diabetes* 66 (3): 674–88. doi:10.2337/db16-0843.

Roelen, C., W. de Vries, H. Koppeschaar, C. Vervoorn, J. Thijssen, and M. Blankenstein. 1997. “Plasma Insulin-Like Growth Factor-I and High Affinity Growth Hormone-Binding Protein Levels Increase After Two Weeks of Strenuous Physical Training.” *International Journal of Sports Medicine* 18 (4): 238–41. doi:10.1055/s-2007-972626.

Roith, D Le, C Bondy, S Yakar, J L Liu, and A Butler. 2001. “The Somatomedin Hypothesis: 2001.” *Endocrine Reviews* 22 (1): 53–74. doi:10.1210/edrv.22.1.0419.

Rosenfeld, Ron G. 2005. “The Molecular Basis of Idiopathic Short Stature.” *Growth Hormone & IGF Research* 15 (July): 3–5. doi:10.1016/j.ghir.2005.06.014.

Rudman, Daniel, Axel G. Feller, Hoskote S. Nagraj, Gregory A. Gergans, Pardee Y. Lalitha, Allen F. Goldberg, Robert A. Schlenker, Lester Cohn, Inge W. Rudman, and Dale E. Mattson. 1990. “Effects of Human Growth Hormone in Men over 60 Years Old.” *New England Journal of Medicine* 323 (1): 1–6. doi:10.1056/NEJM199007053230101.

Salomon, F, R C Cuneo, R Hesp, and P H Sönksen. 1989. “The Effects of Treatment with Recombinant Human Growth Hormone on Body Composition and Metabolism in Adults with Growth Hormone Deficiency.” *The New England Journal of Medicine* 321 (26): 1797–1803. doi:10.1056/NEJM198912283212605.

Salomon, F, and P H Sonksen. 1987. “Physiological Role of GH in Adult Life.pdf.” *ACTA PEDIATR SCAN* 337: 158–63.

Saugy, M. 2006. “Human Growth Hormone Doping in Sport.” *British Journal of Sports Medicine* 40 (Supplement 1): i35–39. doi:10.1136/bjsm.2006.027573.

Schwarz, A J, J A Brasel, R L Hintz, S Mohan, and D M Cooper. 1996. “Acute Effect of Brief Low- and High-Intensity Exercise on Circulating Insulin-like Growth Factor (IGF) I, II, and IGF-Binding Protein-3 and Its Proteolysis in Young Healthy Men.” *The Journal of Clinical Endocrinology and Metabolism* 81 (10): 3492–97. doi:10.1210/jcem.81.10.8855791.

Sheffield-Moore, M, C W Yeckel, E Volpi, S E Wolf, B Morio, D L Chinkes, D Paddon-Jones, and R R Wolfe. 2004. “Postexercise Protein Metabolism in Older and Younger Men Following Moderate-Intensity Aerobic Exercise.” *American Journal of Physiology. Endocrinology and Metabolism* 287 (3): E513-22. doi:10.1152/ajpendo.00334.2003.

Short, Kevin R, Janet L Vittone, Maureen L Bigelow, David N Proctor, and K Sreekumaran Nair. 2004. “Age and Aerobic Exercise Training Effects on Whole Body and Muscle Protein Metabolism.” *American Journal of Physiology. Endocrinology and Metabolism* 286 (1). American Physiological Society: E92-101. doi:10.1152/ajpendo.00366.2003.

Smaniotto, Salete, Alves Martins-neto, and Mireille Dardenne. 2011. “Growth Hormone Is a Modulator of Lymphocyte Migration,” 309–13. doi:10.1159/000329497.

Smit, L S, D J Meyer, N Billestrup, G Norstedt, J Schwartz, and C Carter-Su. 1996. “The Role of the Growth Hormone (GH) Receptor and JAK1 and JAK2 Kinases in the Activation of Stats 1, 3, and 5 by GH.” *Molecular Endocrinology (Baltimore, Md.)* 10 (5): 519–33. doi:10.1210/mend.10.5.8732683.

Solini, Anna, Enzo Bonora, Riccardo Bonadonna, Pietro Castellino, and Ralph A. DeFronzo. 1997. “Protein Metabolism in Human Obesity: Relationship with Glucose and Lipid Metabolism and with Visceral Adipose Tissue [1].” *The Journal of Clinical Endocrinology & Metabolism* 82 (8): 2552–58. doi:10.1210/jcem.82.8.4182.

SOLOMON, J, and R O GREEP. 1959. "THE GROWTH HORMONE CONTENT OF SEVERAL VERTEBRATE PITUITARIES [1]." *Endocrinology* 65 (2): 334–36. doi:10.1210/endo-65-2-334.

Stofega, M R, J Herrington, N Billestrup, and C Carter-Su. 2000. "Mutation of the SHP-2 Binding Site in Growth Hormone (GH) Receptor Prolongs GH-Promoted Tyrosyl Phosphorylation of GH Receptor, JAK2, and STAT5B." *Molecular Endocrinology (Baltimore, Md.)* 14 (9): 1338–50. doi:10.1210/mend.14.9.0513.

Stubbs, W A, G Delitala, A Jones, W J Jeffcoate, C R Edwards, S J Ratter, G M Besser, S R Bloom, and K G Alberti. 1978. "Hormonal and Metabolic Responses to an Enkephalin Analogue in Normal Man." *Lancet (London, England)* 2 (8102): 1225–27.

Surya, Sowmya, Jeffrey F. Horowitz, Naila Goldenberg, Alla Sakharova, Matthew Harber, Andrea S. Cornford, Kathy Symons, and Ariel L. Barkan. 2009. "The Pattern of Growth Hormone Delivery to Peripheral Tissues Determines Insulin-Like Growth Factor-1 and Lipolytic Responses in Obese Subjects." *The Journal of Clinical Endocrinology & Metabolism* 94 (8): 2828–34. doi:10.1210/jc.2009-0638.

Takarada, Y, Y Nakamura, S Aruga, T Onda, S Miyazaki, and N Ishii. 2000. "Rapid Increase in Plasma Growth Hormone after Low-Intensity Resistance Exercise with Vascular Occlusion." *Journal of Applied Physiology (Bethesda, Md. : 1985)* 88 (1): 61–65. doi:10.1152/jappl.2000.88.1.61.

Tan, Sock-Hwee, Albert Lee, Dana Pascovici, Natasha Care, Vita Birzniece, Ken Ho, Mark P. Molloy, and Alamgir Khan. 2017. "Plasma Biomarker Proteins for Detection of Human Growth Hormone Administration in Athletes." *Scientific Reports* 7 (1). Springer US: 10039. doi:10.1038/s41598-017-09968-7.

Tessari, P, S L Nissen, J M Miles, and M W Haymond. 1986. "Inverse Relationship of Leucine Flux and Oxidation to Free Fatty Acid Availability in Vivo." *The Journal of Clinical Investigation* 77 (2): 575–81. doi:10.1172/JCI112339.

Ubertini, G, A Grossi, D Colabianchi, R Fiori, C Brufani, C Bizzarri, G Giannone, et al. 2008. "Young Elite Athletes of Different Sport Disciplines Present with an Increase in Pulsatile Secretion of Growth Hormone Compared with Non-Elite Athletes and Sedentary Subjects." *Journal of Endocrinological Investigation* 31 (2): 138–45. doi:10.1007/BF03345580.

Vahl, N, J O Jørgensen, A G Jurik, and J S Christiansen. 1996. "Abdominal Adiposity and Physical Fitness Are Major Determinants of the Age Associated Decline in Stimulated GH Secretion in Healthy Adults." *The Journal of Clinical Endocrinology and Metabolism* 81 (6): 2209–15. doi:10.1210/jcem.81.6.8964853.

Vahl, Nina, Niels Møller, Torsten Lauritzen, Jens S. Christiansen, and Jens O. L. Jørgensen. 1997. "Metabolic Effects and Pharmacokinetics of a Growth Hormone Pulse in Healthy Adults: Relation to Age, Sex, and Body Composition." *The Journal of Clinical Endocrinology & Metabolism* 82 (11): 3612–18. doi:10.1210/jcem.82.11.4388.

Vance, M L, D L Kaiser, L A Frohman, J Rivier, W W Vale, and M O Thorner. 1987. "Role of Dopamine in the Regulation of Growth Hormone Secretion: Dopamine and Bromocriptine Augment Growth Hormone (GH)-Releasing Hormone-Stimulated GH Secretion in Normal Man." *The Journal of Clinical Endocrinology and Metabolism* 64 (6): 1136–41. doi:10.1210/jcem-64-6-1136.

Vanhelder, W P, M W Radomski, and R C Goode. 1984. "Growth Hormone Responses during Intermittent Weight Lifting Exercise in Men." *European Journal of Applied Physiology and Occupational Physiology* 53 (1): 31–34.

Veldhuis, J D, S M Anderson, N Shah, M Bray, T Vick, A Gentili, T Mulligan, et al. 2001. "Neurophysiological Regulation and Target-Tissue Impact of the Pulsatile Mode of Growth Hormone Secretion in the Human." *Growth Hormone & IGF Research : Official Journal of the Growth Hormone Research Society and the International IGF Research Society* 11 Suppl A (June): S25-37.

Vihervuori, E, M Virtanen, H Koistinen, R Koistinen, M Seppälä, and M A Siimes. 1996. "Hemoglobin Level Is Linked to Growth Hormone-Dependent Proteins in Short Children." *Blood* 87 (5): 2075–81.

Viru, A, K Karelson, and T Smirnova. 1992. “Stability and Variability in Hormonal Responses to Prolonged Exercise.” *International Journal of Sports Medicine* 13 (3): 230–35. doi:10.1055/s-2007-1021259.

Weltman, A., C J Pritzlaff, and L Wideman. 2000. “The Relationship between Exercise Intensity and Growth Hormone (GH) Release Is Attenuated in Older Men.” *Fourth International Conference of the Growth Horm Res Society* Sep 7-9 Go.

Weltman, A, J Y Weltman, R Schurrer, W S Evans, J D Veldhuis, and A D Rogol. 1992. “Endurance Training Amplifies the Pulsatile Release of Growth Hormone: Effects of Training Intensity.” *Journal of Applied Physiology (Bethesda, Md. : 1985)* 72 (6): 2188–96. doi:10.1152/jappl.1992.72.6.2188.

Weltman, A, J Y Weltman, C J Womack, S E Davis, J L Blumer, G A Gaesser, and M L Hartman. 1997. “Exercise Training Decreases the Growth Hormone (GH) Response to Acute Constant-Load Exercise.” *Medicine and Science in Sports and Exercise* 29 (5): 669–76.

Weltman, Arthur, Cathy J. Pritzlaff, Laurie Wideman, Judy Y. Weltman, Jeffery L. Blumer, Robert D. Abbott, Mark L. Hartman, and Johannes D. Veldhuis. 2000. “Exercise-Dependent Growth Hormone Release Is Linked to Markers of Heightened Central Adrenergic Outflow.” *Journal of Applied Physiology* 89 (2): 629–35. doi:10.1152/jappl.2000.89.2.629.

Weltman, Arthur, Judy Y Weltman, Dee Dee Watson Winfield, Kirsten Frick, James Patrie, Petra Kok, Daniel M Keenan, Glenn a Gaesser, and Johannes D Veldhuis. 2008. “Effects of Continuous versus Intermittent Exercise, Obesity, and Gender on Growth Hormone Secretion.” *The Journal of Clinical Endocrinology and Metabolism* 93 (12): 4711–20. doi:10.1210/jc.2008-0998.

Wheldon, Adam, Richard L Savine, Peter H Sönksen, and Richard I G Holt. 2006. “Exercising in the Cold Inhibits Growth Hormone Secretion by Reducing the Rise in Core Body Temperature.” *Growth Hormone & IGF Research : Official Journal of the Growth Hormone Research Society and the International IGF Research Society* 16 (2): 125–31. doi:10.1016/j.ghir.2006.02.005.

Widdowson, W. Matthew, Marie Louise Healy, Peter H. Sönksen, and James Gibney. 2009. “The Physiology of Growth Hormone and Sport.” *Growth Hormone and IGF Research* 19 (4). Elsevier Ltd: 308–19. doi:10.1016/j.ghir.2009.04.023.

Wideman, Laurie, Leslie Consitt, Jim Patrie, Brenda Swearingin, Richard Bloomer, Paul Davis, Arthur Weltman, Brenda Swearin-, and Arthur Weltman The. 2006. “The Impact of Sex and Exercise Duration on Growth Hormone Secretion.” *Journal Applyed Physiology* 27402: 1641–47. doi:10.1152/japplphysiol.00518.2006.

Wideman, Laurie, Judy Y Weltman, Mark L Hartman, Johannes D Veldhuis, and Arthur Weltman. 2002a. “Acute and Chronic Aerobic and Recent Findings” 32 (15): 987–1004.

———. 2002b. “Acute and Chronic Aerobic and Recent Findings.” *Sports Medicine* 32 (15): 987–1004.

Wideman, L, J Y Weltman, N Shah, S Story, J D Veldhuis, and a Weltman. 1999. “Effects of Gender on Exercise-Induced Growth Hormone Release.” *Journal of Applied Physiology (Bethesda, Md. : 1985)* 87 (3): 1154–62.

“World Anti-Doping Program: Human Growth Hormone (hGH) Biomarkers Test for Doping Control Analysis.” n.d.

Yarasheski, K E, J A Campbell, K Smith, M J Rennie, J O Holloszy, and D M Bier. 1992. “Effect of Growth Hormone and Resistance Exercise on Muscle Growth in Young Men.” *The American Journal of Physiology* 262 (3 Pt 1): E261-7. doi:10.1152/ajpendo.1992.262.3.E261.

Yarasheski, K E, J J Zachwieja, J A Campbell, and D M Bier. 1995. “Effect of Growth Hormone and Resistance Exercise on Muscle Growth and Strength in Older Men.” *The American Journal of Physiology* 268 (2 Pt 1): E268-76. doi:10.1152/ajpendo.1995.268.2.E268.

Zaccaria, M., M. Varnier, P. Piazza, D. Noventa, and A. Ermolao. 1999a. “Blunted Growth Hormone Response to Maximal Exercise in Middle-Aged versus Young Subjects and No Effect of Endurance Training.” *Journal of Clinical Endocrinology and Metabolism* 84 (7): 2303–7. doi:10.1210/jcem.84.7.5853.

Zaccaria, M, M Varnier, P Piazza, D Noventa, and A Ermolao. 1999b. “Blunted Growth Hormone Response to Maximal Exercise in Middle-Aged versus Young Subjects and No Effect of

Endurance Training." *The Journal of Clinical Endocrinology and Metabolism* 84 (7): 2303–7. doi:10.1210/jcem.84.7.5853.