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The Research Progress of Growth Hormone and Cardiovascular Disease

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Abstract: *Growth hormone (GH) is a hormone necessary for the growth and development of all organs in the human body and is synthesised and secreted by the pituitary gland. Pituitary diseases can lead to abnormalities in GH secretion. The main manifestations are acromegaly and growth hormone deficiency (GHD). Abnormalities in GH secretion increase the incidence of cardiovascular disease and the risk of cardiovascular death, which reduces the survival and quality of life of patients. Therefore, it is necessary to study the effects of GH on the cardiovascular system. The relationship between GH and the cardiovascular system has attracted much attention, and this article will review the relationship between GH and the cardiovascular system.*

Keywords: *growth hormone, cardiovascular disease, acromegaly, growth hormone deficiency*

1. Introduction

GH is a peptide hormone synthesised and secreted by GH cells in the anterior pituitary gland. GH plays many different roles in the human body, mainly in promoting the growth and development of human organs and in regulating the metabolism of a variety of substances, including proteins, lipids, glucose, water and electrolytes. However, most studies have not found a separate role for GH, but rather a dependence on insulin-like growth factor 1 (IGF-1) for its physiological functions. The GH/IGF-1 axis plays an important role in the maintenance of the structure and function of the cardiovascular system. While GH directly promotes cardiac growth and enhances myocardial contractility, GH/IGF-1 also interacts with the vascular system, e.g., by altering vascular tone or sympathetic activity and thus altering peripheral resistance. [1-2]

Numerous studies have elaborated on the interaction of the GH/IGF-1 axis with the cardiovascular system in the presence of abnormal GH secretion. In patients with excessive GH secretion, represented by patients with acromegaly, it is often combined with abnormalities such as cardiac hypertrophy, hypertension, arrhythmia, and valvular disease; and in patients with reduced GH secretion, represented by GHD, it is often accompanied by abnormalities such as reduced heart mass, impaired cardiac contractile function, and vascular endothelial dysfunction. In this article, we will review the latest research on GH and cardiovascular system.

2. Regulation of GH secretion

GH is a 22 kDa polypeptide hormone transcribed and translated from the GH1 gene on chromosome 17, which is synthesised and secreted by the GH cells in the anterior pituitary gland.GH is secreted in pulses 6-8 times a day, with a strong rhythmic and cyclic pattern, with small pulses starting a few hours after meals and large pulses secreted at the beginning of slow-wave sleep. The GH level reaches a peak at night, with a trough in the morning [3], and the rest of the day's GH secretion is negligible. Growth hormone-releasing hormone (GHRH) and growth suppressor (SS) secreted by the hypothalamus and gastric hunger hormone secreted by intestinal cell precursors are the three most important hormones that directly regulate GH secretion. In addition, GH secretion is directly or indirectly regulated by a variety of hormones and the body's metabolism, such as catecholamines and oestrogens, which can promote GH secretion. Glucocorticoids, insulin, IGF-1, obesity, high free fatty acids, α1 agonists, βagonists, and aging inhibit GH secretion. [4]

Pituitary disease can lead to abnormal GH secretion. Acromegaly is the classic endocrine disorder of GH excess, and more than 95% of acromegaly is due to abnormally high GH secretion from pituitary

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GH adenomas. GH stimulates the liver to produce large amounts of IGF-1, and the excess GH and IGF-1 promote the overgrowth of soft tissues, bone, and cartilage throughout the body, resulting in patients with the classic symptoms of acromegaly. Another typical GH secretion abnormality disease is GHD, which is the insufficient or relative insufficiency of GH secretion caused by pituitary gland dysfunction or GH, IGF-1 receptor defects. Both acromegaly and GHD have been shown to be associated with an increased incidence of cardiovascular disease, as will be discussed below.

3. GH signal transduction

GH binds to its cell surface receptor GH receptor (GHR) to initiate intracellular signaling cascades.[5] GHR is a transmembrane protein belonging to the type 1 cytokine receptor family. The extracellular structural domain of each GHR monomer has two sub-structural domains, sub-structural domain 2 promotes the formation of dimers by GHR monomers, and sub-structural domain 1 contains most of the GH contacts, and the GHR dimer undergoes a conformational change that triggers signaling when GH binds to the GHR dimer as a ligand.[6] Growth hormone binding protein (GHBP) is the soluble part of the extracellular structural domain of GHR, which is cleaved by the metalloproteinase TNF-converting enzyme and enters the serum, and the binding of GH to GHBP significantly prolongs the half-life of GH. [7]

Binding of GH to GHR leads to the activation of several downstream signaling pathways within the cell. The most important is the activation of the JAK/STAT signaling pathway, which promotes the transcription of a variety of genes, such as IGF-1, IGF-binding protein 3 (IGFBP3) and IGF-2.[5, 8] Abundant GHR exists in the liver, and GH stimulates the liver to produce most of the body's IGF-1, which is a single-chain protein structurally homologous to insulin. IGF-1 binds to IGF-binding proteins (IGFBPs) in the blood circulation to form a complex that prevents the rapid clearance of IGF-1, and is transported to tissues throughout the body by endocrine means, where it binds to IGF-1R After binding to IGF-1R, it exerts a growth-promoting effect through the PI3K/Akt signaling pathway; other tissues may also secrete a small amount of IGF-1, which can function in an autocrine or paracrine manner. [9]

4. Mechanism of action of GH on the cardiovascular system

The GH/IGF-1 axis exerts important effects on the cardiovascular system through multiple pathways. Both myocardial and vascular endothelial cells express GHR [10] and IGF-1R [11-12], and can locally produce IGF-1 [11, 13]. GH can act directly on the heart and blood vessels or through the endocytosis, autocrine and paracrine secretion of IGF-1, etc. GH can play an important role in various aspects of the cardiovascular system, including promoting cardiac growth, enhancing cardiac contraction, regulating vascular tone and peripheral resistance, and affecting the metabolism of cardiovascular risk factors such as blood lipids, blood glucose, and insulin.

4.1 GH and heart structure

Both in GH-deficient and GH-overdosed patients, studies have found relevant alterations in cardiac structure, confirming the importance of GH in maintaining cardiac structure.

Cardiomyocytes, as definitive terminally differentiated cells, respond to GH/IGF-1 stimulation through remodeling and hypertrophy. A few studies have demonstrated that GH can exert direct effects on cardiomyocytes independently of IGF-1 [14], altering cardiomyocyte metabolism and promoting cardiomyocyte growth. In addition, GH and IGF-1 promote the transcription of similar muscle-specific genes, e.g., GH independently induces cardiac c-fos, myosin light chain-2, and α-actin-specific gene transcription [15], and also increases cardiac troponin I, myosin light chain-2 [16], and α-actin gene transcription by inducing IGF-1. The GH/IGF-1 axis is mediated by increased amino acid uptake and cellular protein synthesis as well as stimulating muscle-specific gene transcription, leading to cardiomyocyte hypertrophy [14, 17].

Cardiac hypertrophy is accompanied by cardiac remodeling and the extracellular matrix has been the focus of several studies.IGF-1 promotes collagen synthesis by fibroblasts [17], while GH increases the rate of collagen deposition in the heart [18]. The volume fraction of collagen was found to be normal in GH-induced cardiac hypertrophy, suggesting that collagen synthesis and catabolism are consistent leading to a constant cardiac collagen concentration [1]. However, there is still a lack of evidence on how GH and IGF-1 increase collagen catabolism and that cardiac replacement fibrosis is significantly increased in

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patients with acromegaly.

In addition to promoting cardiomyocyte growth, inhibition of cardiomyocyte apoptosis by IGF-1 has been confirmed by numerous studies. In cardiac ischemia-reperfusion models, extensive studies have confirmed that IGF-1 inhibits apoptosis through the PI3K/Akt pathway [19]. The use of IGF-1 in cardiac progenitor cell therapy can effectively promote angiogenesis and inhibit apoptosis, thus increasing the number of regenerating cardiomyocytes [20].

4.2 GH and cardiac contractility

Several in vitro studies have demonstrated that IGF-1 has a direct effect on myocardial contractility [21-22], and that IGF-1 increases transient intracellular Ca2+ concentration in cardiomyocytes in vitro by acutely increasing the L-type Ca2+ channel activity [21,23]. At the same time, IGF-1 up-regulates the sarcoplasmic reticulum ATPase (SERCA2) level [24], and SERCA2 induces sarcoplasmic reticulum reuptake of Ca2+, increasing peak sarcoplasmic reticulum Ca2+ reserve and thus myocardial contractility reserve. It has also been demonstrated that IGF-1 increases sensitivity of myofilaments to Ca2+ without increasing Ca2+ concentration [22]. Although GH has no effect on short-term Ca2+influx, long-term treatment with GH increases peak Ca2+levels in cardiomyocytes; GH improves energy metabolism, converting metabolic energy to internal work and increasing the intrinsic force-producing capacity of myofilaments; GH induces the conversion of myosin to the V3 isoform, which is low in ATPase activity [25], increases protein calcium sensitivity, and allows the myocardium to function with lower energy.

4.3 GH and blood vessels

GH/IGF-1 can affect the vascular system by acting on endothelial cells, smooth muscle cells (SMC) or macrophages.

It has been demonstrated that GHR and IGF-1R are present on endothelial cells, suggesting that endothelial cells can be influenced by GH/IGF-1. Since GH and IGF-1 are closely related, demonstrating an independent action of GH independent of IGF-1 is difficult. However, it has been shown that GH can independently regulate endothelial nitric oxide synthase (eNOS) activity, and when GH was injected locally into the human brachial artery, it dramatically increased NO release from forearm vessels without affecting forearm or systemic IGF-1 levels [26]. GH and IGF-1 activate the production of nitric oxide (NO) by eNOS in vascular endothelial cells via the PI3K/Akt pathway [27]. The increase in NO in turn exerts anti-oxidative stress, reduces vascular tone, and affects angiogenesis [28-29]. GH treatment of AGHD patients reduces vascular inflammatory factors [30], and IGF-1 is involved in post-inflammatory angiogenesis [31] and repair [30]. However, GH levels appear to need to be maintained within a physiological range, and similar results were found in the aortas of hypopituitary Ames dwarf mice and GH overexpressing transgenic mice, promoting ROS production and inhibiting the expression of antioxidant enzymes (e.g. glutathione peroxidase and eNOS). Because IGF-1R is expressed in endothelial cells, IGF-I also mediates the proangiogenic effects of GH [32]. Local infusion of IGF-I plasmid into skeletal muscle tissue after ligation of the femoral artery in mice resulted in angiogenesis and increased blood flow to the affected muscle [33]. Several studies have shown that IGF-I is a strong inducer of angiogenesis in different tissues, including the brain [11, 34, 35], protecting them from ischemia-induced apoptosis and inducing local expression of vascular endothelial growth factor [36].

GH/IGF-1 promotion of smooth muscle cell proliferation and migration has been demonstrated in a variety of models [11, 37, 38]. IGF-1 enhances human saphenous vein smooth muscle cell proliferation through the PI3K-Akt/PKB pathway, leading to subsequent intimal thickening and vein grafting [37]. The fact that IGF-1 deficiency attenuated the formation of hypoxic pulmonary vascular remodeling in neonatal mice also illustrated the proliferative effect of IGF-1 on smooth muscle cells [38]. However, in SMC-specific overexpressing Apoe-/- mice, IGF-1 appeared to not only promote SMC proliferation, but also altered the direction of SMC differentiation from contractile to synthetic SMCs, which improved plaque stability, although it did not alter arterial plaque load.

Macrophages, as important immune cells in the body, are involved in the regulation of endothelial proliferation, angiogenesis and repair [39]. Macrophages are subject to the action of IGF-1 from paracrine and autocrine sources [40]. IGF-1 activates integrin-mediated macrophage migration through the PI3K/PKC/p38 MAP pathway [40]. In a model of palmitate-induced macrophage injury, IGF-1 protects macrophages from apoptosis by inhibiting mitochondrial autophagy [41]. This seems to suggest that IGF-1 promotes vascular inflammation via macrophages, but IGF-1 and IGFBP-3 complexes have been found to attenuate pro-inflammatory acute phase responses in patients with severe burns in clinical studies [42].

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Consistent with this, IGF-1 reduces 12/15-lipoxygenase-mediated lipid oxidation and foam cell formation in macrophages [43]. Due to the degrading activity of IGF-1, it may be difficult to estimate the actual bioavailability of IGF-1 in in vitro experiments. Therefore, the effect of IGF-1 on macrophages still needs further investigation.

In addition, IGF-1-induced vasodilation has also been confirmed in studies, such as IGF-1 can induce vasodilation by increasing vascular smooth muscle Na+ -K+ ATPase activity and increasing vascular smooth muscle ATP-sensitive inwardly rectifying K+ channel gene expression [1]. GH replacement therapy (GHRT) reduces sympathetic neural activity in patients with GHD [44] and decreases peripheral vascular resistance. However, some studies have demonstrated that GH plays a role of sympathetic excitation [45].

4.4 GH and cardiovascular risk factors

GH/IGF-1 also has an effect on cardiovascular risk factors, such as glucose-lipid metabolism, insulin resistance, and inflammatory factors. GH promotes lipolysis, decreases low-density lipoprotein cholesterol (LDL-C) levels, increases high-density lipoprotein cholesterol (HDL-C) levels, elevates blood glucose, and modulates inflammatory factor concentrations. The effect of GH on adipose tissue may be mediated by activation of β3-adrenergic receptors, thereby increasing adipose tissue-sensitive lipase (HSL) activity, promoting lipolysis, increasing free fatty acid production, and decreasing lipid mass [46]. GH increases cholesterol 7α-hydroxylase expression and activity, upregulates hepatic LDL-C receptor expression, promotes hepatic uptake of LDL-C, and decreases circulating LDL-C [47]. GH promotes cholesteryl ester transfer protein (CETP) activity and promotes the transport of cholesterol to triglyceride (TG) between lipoproteins, resulting in increased HDL-C. IGF-1 inhibits SRB1 receptor expression on the surface of hepatocytes, elevating circulating HDL-C [48]. The level of IGF-1 shows a U-shaped inverse curve with the insulin resistance index, HOMA-IR, and both excess and decreased IGF-1 decrease insulin sensitivity, inhibiting the glucose uptake by peripheral tissues, increase hepatic glycogenolysis, and elevate circulating glucose levels [49]. Chronic GH overdose and adult GHD patients both lead to a chronic inflammatory state, resulting in elevated levels of circulating pro-inflammatory factors such as tumor necrosis factor (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) [50].

5. GH and cardiovascular diseases

5.1 Cardiovascular damage from GH overdose

Acromegaly is a clinical syndrome characterized by chronic GH and IGF-1 overdose, in which prolonged exposure of the organism to conditions of GH overdose leads to progressive somatic deformities and a wide range of systemic manifestations, including complications of the cardiovascular system, respiratory system, and osteoarthritic morphology. Cardiovascular complications have long been recognized as the leading cause of death in patients with acromegaly. Not only do approximately two-thirds of patients have symptoms associated with cardiovascular complications at the time of diagnosis of acromegaly, but approximately 90% of patients will eventually develop cardiovascular complications during their lifetime. [51]

5.1.1 Acromegaly cardiomyopathy

Acromegaly hypertrophic cardiomyopathy is a morphological and functional alteration of the myocardium secondary to acromegaly and can occur in the absence of other risk factors [52]. Acromegalic cardiomyopathy is characterized by ventricular hypertrophy, which is present in approximately 20% of patients with acromegaly at the time of diagnosis, and ultimately in up to 90% of patients with acromegaly [53]. Acromegalic cardiomyopathy is typically characterized by concentric hypertrophy of the bilateral ventricular wall, but left ventricular and septal hypertrophy are more common [54]. Excessive GH promotes the assembly of new muscle segments resulting in enlarged cardiomyocytes, which present as centripetal hypertrophy [55]. At the same time, histology demonstrates an extensive accumulation of interstitial fibrosis, which is a characteristic histological manifestation of acromegaly cardiomyopathy. The accumulation of fibrosis leads to impaired ventricular diastolic function but does not affect systolic function. In line with this, an echocardiographic study of patients with acromegaly found that left ventricular diastolic function was significantly reduced in patients with acromegaly, but left ventricular ejection fraction was reduced in less than 3% of patients with acromegaly [56]. The severity of acromegaly cardiomyopathy is usually determined by aging and duration of acromegaly, but comorbid hypertension and metabolic complications also significantly exacerbate myocardial hypertrophy [57].

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The course of acromegaly cardiomyopathy is divided into three main stages. The early stage manifests a hyperdynamic state, which is reversible and is mainly characterized by left ventricular wall thickening, normal or increased myocardial contractility and cardiac output, and no diastolic dysfunction. The intermediate stage is characterized by biventricular thickening and diastolic dysfunction, including prolonged isovolumic diastolic time, reduced diastolic filling waves, and increased blood regurgitation during atrial contraction. In the late stage, it will develop into congestive heart failure, which is mainly manifested by systolic and diastolic dysfunction [58].

5.1.2 Hypertension

Hypertension is considered to be the most common complication of acromegaly, but the prevalence of hypertension in acromegaly populations varies widely in different studies, ranging from approximately 17.5%-80% [59], which may be related to differences in the method of blood pressure measurement, criteria for the diagnosis of hypertension, genetics or lifestyle of the study population, and sample size. Although it has been suggested that the use of in-office blood pressure may overestimate the prevalence of hypertension in patients with acromegaly, Minniti et al. found that the prevalence of hypertension in patients with acromegaly diagnosed using in-office blood pressure was 17.5%, whereas the result obtained using 24-hour ambulatory blood pressure testing was 42.5% [60]. Fabiola et al. found similar results that the prevalence of hypertension in patients with acromegaly diagnosed using in-office blood pressure was 32%, whereas the result obtained using 24-hour ambulatory blood pressure testing was 23% [61]. The blood pressure pattern in patients with acromegaly is mainly non-dipping blood pressure [62], i.e., the fall in blood pressure at night is reduced or lost compared to normal, which may be related to sleep apnea syndrome and higher GH levels [59].

The development of hypertension in acromegaly is associated with increased plasma volume. Long-term studies have confirmed that excess GH and IGF-1 lead to sodium retention and a significant increase in plasma volume. However, the mechanism leading to sodium retention is still controversial. Most studies suggest that long-term elevated levels of GH and IGF-1 act directly on renal GHR and IGF-1R, affecting distal tubular epithelial sodium channel (ENaC) activity and promoting water and sodium storage [63]. Kamenicky et al. found that rats and humans with acromegaly had an increased response to amiloride, an ENaC blocker, and an increased response to tachyzoite (Henle NKCC2 inhibitor in the loop) decreased response [64]. Also, GH can directly stimulate the transcriptional regulation of the subunits of ENaC independently of IGF-1 [65], and it is also flanked by the fact that GH/IGF-1 overdose leads to sodium retention. Another view is that GH/IGF-1 may indirectly affect water and sodium reabsorption through the renin-angiotensin-aldosterone system (RAAS) [66]. The presence of RAAS stimulation was demonstrated in two studies: increased aldosterone excretion in pituitary resected rats and in humans after administration of pituitary extracted GH [66]. And biosynthesis of human GH induced an increase in renin activity and aldosterone levels in healthy men [67]. The involvement of RAAS in GH-mediated water and sodium retention was also demonstrated by the elimination of GH-induced increases in extracellular fluid volume by ACEI and aldosterone antagonists in another study [68]. Aldosterone concentrations are increased in patients with presurgical and in transgenic mice, because IGF-1 is suppressed by IGFBP2 overexpression, indicating that GH directly causes aldosterone elevation [69]. However, this view is contradicted by a number of studies, the most direct evidence coming from the fact that GH treatment-induced sodium retention can occur in the absence of the adrenal glands [66]. It has also been suggested that angiotensin II and aldosterone levels are not elevated after GH treatment [70]. And the reduction in aldosterone concentrations in rats with acromegaly also contradicts this view [71]. Other ideas have been proposed, but these are less well studied, such as GH overdose mediating sodium retention through atrial natriuretic peptide (ANP) [70].

Most studies have concluded that GH and IGF may be the main cause of hypertension in patients with acromegaly, either through direct action or indirect action through the RAAS leading to sodium retention. However, other studies have suggested that insulin resistance and hyperinsulinemia, increased sympathetic tone, abnormal vascular endothelial cell function, and obstructive sleep apnea have an effect on the development of hypertension in patients with acromegaly [59].

5.1.3 The coronary artery disease

Although GH is associated with IGF-1 and many atherosclerotic risk factors, such as hypertension, insulin resistance, and hyperlipidaemia, studies on the association between acromegaly and coronary artery disease are scarce and controversial. Several retrospective studies and national registries have reported the prevalence of coronary artery disease in different countries for acromegaly [72], ranging from 2.5% in a cohort in Italy, to 8% in a tertiary center in Mexico, to 7% in Belgium, and 12% in France. Due to the differences in the populations studied and their cardiovascular risk factors, as well as the

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differences in diagnostic criteria in different countries, there is a great deal of controversy regarding the prevalence of coronary artery disease in acromegaly. There is considerable heterogeneity in the prevalence of coronary artery disease.

Due to the low prevalence of acromegaly, few studies have been able to include adequate sample sizes of patients with comorbid coronary artery disease, so some studies have used the Framingham Risk Score (FRS) and the Coronary Calcification Score (CS) or assessed the risk of coronary artery disease in their analyses. Several studies have shown that FRS and CS do not differ significantly between patients with acromegaly and normal population or non-acromegaly patients [73-75]. However, risk scores are predictive of coronary artery disease, and there is still a lack of longer-term prospective studies to validate them.

Other studies have assessed the degree of carotid atherosclerosis by ultrasound measurement of carotid intima-media thickness (IMT), and several studies have demonstrated that IMT is significantly higher in patients with acromegaly than in the normal population [76-79], but some contradictions remain between these studies, with two of them concluding that, compared to matched healthy controls or patients with inactive acromegaly, patients with active acromegaly in which IMT was increased [77-78]. However, two other studies found no significant change in IMT in patients with acromegaly compared to matched control subjects [76, 79]. Although contradictions remain regarding whether GH excess independently affects coronary artery disease, it is undeniable that patients with acromegaly are at increased risk of atherosclerosis through other cardiovascular risk factors.

Several other studies have supported the involvement of IGF-1 in coronary artery disease, such as Sara et al. who found increased coronary microvascular dysfunction in patients with acromegaly by assessing coronary flow reserve (CFR) in patients without cardiovascular symptoms of acromegaly [80]. Yousefzadeh et al. found that the level of IGF-1 correlated with the number of involved coronary arteries [81]. However, in a recent study, cholesterol-fed rabbits were injected intravenously with either IGF-1 or IGFBP-2 or saline for 10 weeks and found that IGF-1 significantly inhibited coronary plaque formation and may significantly inhibit macrophage accumulation through its anti-inflammatory properties, whereas IGFBP-2 exerted the opposite effect on atherosclerosis. There is still a lack of multi-center prospective clinical studies elucidating the relationship between acromegaly and coronary atherosclerotic disease.

5.1.4 Other cardiovascular diseases

Previous studies have shown that patients with acromegaly often have cardiac valve disease, with the mitral and aortic valves being the most common sites of involvement, which is mainly characterized by valvular regurgitation. Most valve disease is mild, Colao et al. found that 86% of patients with active acromegaly had valvular abnormalities, however the degree of valve disease observed was mild to moderate, and the authors did not evaluate whether pathological valvular regurgitation was increased in patients with acromegaly [82]. Pereira, et al. evaluated pathological valvular regurgitation in patients with acromegaly. The study included 40 patients with acromegaly and 120 control patients matched for age, sex, and cardiovascular risk factors, of whom 30% had aortic regurgitation and 5% of patients with acromegaly developed moderate or more mitral regurgitation [83].

The risk of valvular disease increases with the duration of active acromegaly, which may be associated with excess GH and IGF-1 promoting cardiac hypertrophy and fibrosis. A prospective study found that the incidence of mitral regurgitation increased significantly with disease duration in patients with active acromegaly and did not increase in patients with acromegaly in remission [84], suggesting that controlling GH and IGF-1 may be able to mitigate the progression of valve disease. However, few studies have evaluated the risk factors for valve disease, and more research is still needed regarding the mechanisms of valve disease complicating acromegaly.

Several reviews and guidelines have suggested that patients with acromegaly are at higher risk of arrhythmias [85], and that patients with severe left ventricular hypertrophy and myocardial fibrosis may be at increased risk of arrhythmias [86]. Several studies have proposed that patients with acromegaly have a higher incidence of arrhythmias. One such study from Russia found that 42% of patients with acromegaly suffered from arrhythmias and cardiac conduction disturbances, and 61% of patients with arrhythmias who received CMRI had signs of myocardial fibrosis [87]. Warszawski et al. looked at 36 patients with acromegaly, and did not detect persistent arrhythmias, nor were arrhythmia-related symptoms observed [88]. This phenomenon may be related to the absence of significant myocardial fibrosis or myocardial hypertrophy, indirectly suggesting that acromegaly may increase the prevalence of arrhythmias through myocardial fibrosis. However, another study did not report clinically significant arrhythmias in patients with active acromegaly monitored with 24-hour ambulatory electrocardiograms

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[89]. Although some studies have reported a correlation between acromegaly and arrhythmias, more high-quality data and studies on the mechanisms involved are needed to demonstrate that acromegaly increases the prevalence of arrhythmias.

5.2 Cardiovascular damage in GH deficiency

Although GHD has been shown to increase cardiovascular mortality, there are not many studies on the cardiovascular complications of GHD.GH replacement therapy has been shown to ameliorate some of the cardiovascular morbidity and cardiovascular risk in patients with hypopituitarism [90-91].

5.2.1 Hypertension

It is difficult to study the effect of GH on blood pressure in isolation because many factors influence the regulation of blood pressure. Blood pressure is related to other factors such as lipid metabolism, body composition, fat distribution and cardiac function, all of which have been shown to be affected by GH [92-93]. Whether GHD affects blood pressure is still highly controversial. The study with the largest sample size was one that included 926 adult GHD patients, which found that the prevalence of hypertension was 22.6% and 21.7% in male and female GHD patients, respectively, and was significantly higher than in the control population [94]. However, other studies have reported no change in blood pressure [95], and in a study of GHD consisting mainly of young adults, lower blood pressure was found [96].

Because blood pressure is affected by a variety of factors, studies on the relationship between GHD and blood pressure are inevitably contradictory. Some researchers have attempted to help illustrate the relationship between GHD and blood pressure by demonstrating whether GHRT improves hypertension. One meta-analysis, which included 10 trials in which blood pressure monitoring was performed, found a reduction in DBP but not SBP after GHRT [92]. Another group of studies followed the effects of GHRT for 7 years and found a significant reduction in resting DBP but a slight increase in SBP compared to the control group. However, it may be due to age related changes as elevated SBP was also observed in the control population. In addition to this, Abdu et al. found a significant decrease in both BP indices after 6 and 12 months of follow-up. Combined with improvements in lipid profiles, body fat distribution and alternative measures of endothelial dysfunction, these metrics correspond to absolute and relative risk reductions for coronary artery disease, as calculated by the Framingham risk equation [97]. Although it remains unclear whether GHRT reduces SBP, the fact that GHRT reduces DBP seems to be recognized by most studies. In addition to this, GHRT improves body composition, lipids, cardiac and vascular function, making it difficult to isolate the effects on blood pressure. However, GHRT does reduce overall cardiovascular mortality in patients with GHD, and further research is necessary to study the relationship between GHD and hypertension to help the clinical application of GHRT.

5.2.2 Reduced heart mass

Physiological levels of GH are important for normal myocardial growth, and in echocardiographic studies associated with GHD, reductions in cardiac mass, including reductions in LVMi and LV diameter, and reductions in LVW and IVS thickness, have been observed. However, these findings appear to be consistent only in cGHD [96], and the effect of GH deficiency on cardiac mass is controversial in adult patients with GHD [98], but appears to have some effect on cardiac function. One study found systolic dysfunction in young GHD patients both at rest and after exercise [99]. Subsequent studies have found that this impairment of cardiac function is not only present in young patients, but similar findings have been reported in middle-aged and even elderly GHD patients [100]. Taken together, this evidence suggests that GHD is commonly associated with reduced heart mass and impairment of systolic function, especially after physical activity. However, it remains to be determined whether the severity of cardiac damage in GHD is dependent on the patient's age and/or age of onset, or more likely on the severity of the disease.

Most studies have shown an improvement in heart quality during GHRT [101]. In addition to its effects on heart mass, GHRT induces improvements in cardiac function. Improvements in systolic and diastolic function, observed after 6 months of follow-up, persisted after several years of GHRT treatment and appeared to be more sustained in CoGHD patients than in AoGHD patients, which may be related to the improvement in cardiac mass decline during GHD in children [102].

5.2.3 The coronary artery disease and cardiovascular risk factors

Boschetti et al. found in a small sample of GHD patients a reduced CFR compared to matched controls [103]. Several studies have addressed IMT, in one of which Leonsson et al. observed that increased IL-6 was independently associated with IMT in GHD patients. In contrast, the resultant IGF-1 was

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negatively, but not independently, correlated with IMT [104]. Another study analyzed 14 patients with GHD treated with GH and found that after 12 months of GH treatment, there were no significant changes in IMT and related inflammatory markers, but endothelial function was significantly improved [105]. A Japanese retrospective study included 110 patients with GHD in the analysis [106], and IMT was performed in 33 patients, with abnormalities, including increased IMT or plaque, observed in 8 patients. However, this study did not include a matched control population to know whether GHD caused IMT thickening. This study also reported hypercholesterolemia in 41% of adults with GHD, hypertriglyceridemia in 41%, reduced HDL cholesterol levels in 47%, and increased LDL cholesterol levels in 48%. Diabetes mellitus and impaired glucose tolerance were found in 4 patients with CoGHD and 16 patients with AoGHD. Insulin resistance was assessed in 36 patients by the homeostasis model insulin resistance index (HOMA-R), and the HOMA-R was significantly greater than the mean of normal subjects. These studies may indicate that GH does not have a direct effect on atherosclerosis, but rather promotes atherosclerosis indirectly by altering metabolism, inflammatory factors, insulin resistance, and other cardiovascular risk factors.

Although there is still a lack of clinical trials on the association of GHD with the incidence of coronary artery disease, there are a number of studies demonstrating the relationship between GHD and cardiovascular risk factors such as lipid metabolism, inflammatory factors and insulin resistance.

Many studies have found dyslipidemia in GHD patients to be elevated levels of total cholesterol (TC) and LDL-C, which are also well-known risk factors for atherosclerosis [107-108]. Reduced HDL-C levels have also been suggested in some studies [103, 107]. Since many patients with hypopituitarism have, not only GH deficiency, but also deficiencies of other hormones, it is difficult to distinguish whether altered lipid metabolism is due to GH or other hormones. Patients with isolated GHD have been the subject of analysis in several studies. Several studies included analyses of GHD patients with impaired GHRH receptors [109], male patients with isolated GHD [108], and patients with isolated GHD of different etiologies from the KIMS database [110], and came to the same conclusions, that GHD patients had increased TC and LDL-C, and no significant changes in TG and HDL-C, compared to the control populations of the respective studies. These data were also demonstrated in GHRT, where the effect of GHRT on lipids was comprehensively summarized in a meta-analysis by Maison et al. which concluded that TG and LDL-C were significantly reduced after GHRT.

Patients with GHD experience changes in body composition, mainly a decrease in lean body mass and an increase in visceral obesity [111], which characterize the metabolic syndrome (MetS) and are strongly associated with insulin resistance and glucose intolerance. Although basal insulin levels in adult GHD patients are controversial, Johansson et al [112] found that despite normal fasting glucose and insulin levels, insulin sensitivity was 2-3 times lower in GHD patients compared to controls. In addition, other cardiovascular risk factors are present in patients with GHD, CRP has been reported to be about 4-5 times increased in patients with GHD [113], and elevated levels of pro-inflammatory factors, such as interleukin (IL-6) and tumor necrosis factor (TNF)-α, have also been reported in several studies [104, 113]. It is suggested that a chronic pro-inflammatory state may exist in GHD patients.

There is still a lack of prospective trials in GHD patients with cardiovascular disease incidence as an observational endpoint, and although most studies of GHD and cardiovascular risk factors can be consistent, there is a great deal of heterogeneity in observational studies of the relationship between GHD and cardiovascular disease. Since GHRT has been shown to improve symptoms well in patients with GHD, it may make more clinical sense to focus studies on the role of GHRT on cardiovascular disease.

6. Summary

The mechanism of GH action on the cardiovascular system has been interpreted in three main ways: the structure of the heart, myocardial contractility, and blood vessels. However, other factors such as glucose and lipid metabolism, inflammatory factors, and other hormones may affect the cardiovascular system, and the relationship between GH and cardiovascular disease may be a "U-shaped" one, i.e., excessive or insufficient GH can cause cardiovascular damage, and maintaining a certain range of GH/IGF-1 levels may be the optimal solution to maintain a normal heart. Although it is well established that alterations in GH are associated with increased cardiovascular mortality, GH and the incidence of cardiovascular disease remain highly controversial. Many studies have provided some relevant evidence by demonstrating the association of GH or GHRT with cardiovascular risk factors. Due to the low prevalence of acromegaly and GHD, multicenter prolonged prospective studies on the relationship between GH and cardiovascular disease are the best way to address this issue.

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