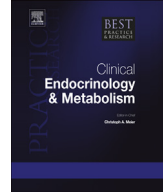




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### Cardiovascular alterations in adult GH deficiency

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There is a growing body of evidence indicating that patients with adult GH deficiency (GHD) are characterized by a cluster of traditional and emerging cardiovascular risk factors and markers, which can significantly increase their cardiovascular morbidity and mortality possibly linked to aberrations in GH status. Patients with adult GHD present multiple different cardiovascular abnormalities. In addition, cardiovascular risk in adult GHD is increased due to altered body composition, abnormal lipid profile, insulin resistance and impaired glucose metabolism. Cardiovascular risk factors can be reversed, at least partially, after GH replacement. However, evidence on the effects of GH replacement on cardiovascular events and mortality is too limited in adult GHD patients. Aim of this review is to provide an at-a-glance overview of the role of the GH/IGF-I on the cardiovascular system and the state of art of the effects of GH replacement on cardiovascular system.

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## Introduction

GH is principally involved in the regulation of somatic growth, including cardiac development and function, and exerts its effects either directly or indirectly by stimulating the production of its tissue effector insulin-like growth factor-1 (IGF-I), which ultimately mediates GH actions on peripheral tissues. In particular, GH/IGF-I axis plays an important role in cardiac growth, myocardial contractility and vascular system. Abnormalities of the GH/IGF-I axis contribute in determining cardiovascular disease, as suggested by clinical studies reporting an increased risk for cardiovascular morbidity and mortality both in GH deficiency (GHD) and excess [1–4].

## Physiological effects of GH on cardiovascular system

As reported in previous reviews, the relationship between GH/IGF-I axis and cardiovascular system has been demonstrated by several experimental studies [4,5]. In physiological conditions, GH/IGF-I axis exerts relevant cardiovascular actions aimed to regulate cardiac growth and myocardial contractility, thus contributing to the maintenance of cardiac mass and function in normal adults [4]. Functional receptors for GH and IGF-I are also expressed in blood vessels [6]. Thus GH/IGF-I axis interacts specifically with the vascular system regulating the vascular tone and the peripheral resistance [4], which indirectly affects cardiac performance [5]. In addition, GH upregulates the myocardial expression of IGF-I mRNA [6]. Besides direct actions of GH, endocrine or autocrine/paracrine effects of locally produced IGF-I on the cardiovascular system are likely operating as well, thus making it difficult to differentiate between the direct effects of GH and those IGF-I-mediated [7].

GH and IGF-I receptors expressed in cardiomyocytes are responsible for direct actions of both hormones on cardiac growth and metabolism. However, the vast majority of the studies have failed to show direct, IGF-I-independent hypertrophic effects of GH on cardiomyocytes [4]. In contrast, experimental models clearly demonstrated that IGF-I *per se* causes hypertrophy of cultured rat cardiomyocytes [8]. The increased cardiac protein synthesis is mainly mediated by the activation of the phosphatidylinositol 3-kinase (PI3K)–Akt pathway, one of the two major pathways of IGF-I signalling [9], and by delaying cardiomyocyte apoptosis [10]. GH and IGF-I also have direct effects on myocardial contractility and cardiac output in both humans and experimental animals. These effects are mediated by the increased mRNA expression for specific muscle proteins, including troponin, myosin light chain-2, and  $\alpha$ -actin [4,5]. GH promotes the shift toward the V3 myosin isoform with lower ATPase activity, which may decrease the energy demand of the contractile process [4,5,11]. In addition, GH and IGF-I increase both intracellular calcium content and calcium sensitivity of myofilaments in cardiomyocytes [4,11]. The endothelial cells have high-affinity binding sites for IGF-I. In particular, the local production of IGF-I causes endothelial dependent vasodilatation via the stimulation of the nitric oxide (NO) production [4]. Moreover, IGF-I may cause vasodilatation through non-endothelium-dependent actions, by increasing the activity of the Na<sup>+</sup>, K<sup>+</sup>–ATPase in vascular smooth muscle cells [12], with possible contribution of increased gene expression of the vascular smooth muscle ATP sensitive potassium channels [4].

## Effects of GHD on cardiovascular risk factors and system in adult patients

The relationship between the GH/IGF-I axis and the cardiovascular system is well confirmed by cardiac functional and morphological abnormalities presented by patients with both GH excess and deficiency [1–4]. In particular, patients with hypopituitarism have reduced life expectancy, with a 2-fold higher risk of death for cardiovascular disease compared with healthy controls [13]. It is conceivable that the excessive glucocorticoids or T4 replacement, or gonadal steroids under-replacement can potentially contribute to the increased cardiovascular mortality in hypopituitary patients. Nevertheless, when all other pituitary hormones have been adequately replaced, GHD can be ultimately considered the underlying determinant for the increased mortality observed in these patients [2–4,13]. GHD-mediated negative effects on the cardiovascular function are played both directly on the myocardium and endothelium, and indirectly *via* increased cardiovascular risk factors, hypercoagulability, decreased exercise performance and reduced pulmonary capacity [2–4,14].

In experimental models [15], hypophysectomy decreases the size of several organs, including the heart, which is reversed by GH administration. GHD patients present different abnormalities in cardiac size and function [2–4]. A significant reduction in the thickness of the left ventricular (LV) posterior wall and of the interventricular septum is reported in both children and adolescents with GHD and in GHD adults, resulting in a decrease of LV mass index (LVMI) and LV internal diameter in these patients [2–4]. Other studies showed, however, a similar cardiac function and morphology between patients developing GHD in adult age (AoGHD) and controls [2–4]. In particular, the decrease in cardiac mass is uncommon in middle-aged or elderly patients, and even in young patients with AoGHD, while it can be mainly observed in young patients with childhood-onset (Co) GHD [16]. Similarly, the so-called hypokinetic syndrome, which is characterized by a decrease in heart rate and systolic performance, was observed only in young GHD patients with CoGHD [2,3]. It should be noted that echocardiography is not a method sensitive enough to reveal subtle deficiency in LV performance. Using the equilibrium radionuclide angiography, our group first reported an impairment of LV performance in response to exercise in most adult GHD patients, regardless of age and age of disease onset [2,3,16]. We found also that cardiac performance was correlated with the GH status, as a significant functional impairment could be evidenced in patients with severe and partial GHD, but not in non-GHD hypopituitary patients [17].

More recently, Boschetti et al. [18] found in a small sample of GHD patients that the coronary flow reserve (CFR), an early marker of impaired myocardial microcirculation that may be present before manifest atherosclerosis and stenosis occur, was significantly decreased as compared to matched controls. New methodologies, such as 2D speckle-tracking echocardiography (2DSTE) [19], have proven to be more sensitive for the detection of subclinical LV dysfunction in several conditions with preserved LV ejection fraction (EF) [20,21]. In this regard, Mihaila [22] recently reported that adult GHD have LV systolic function, assessed by conventional echocardiography, within the normal range, whereas LV longitudinal, circumferential, and torsion functions, assessed by 2DSTE, were impaired, which is suggestive of intrinsic myocardial disease in these patients. Thus, the use of traditional methods of assessment of cardiac impairment might show limited diagnostic accuracy in defining the effects of GHD on cardiac mass [23]. Cardiac magnetic resonance (CMR) imaging, a reliable and reproducible technique for measuring myocardial volume, mass and function, has been used to study a range of cardiomyopathies [24,25]. Currently, there are only few CMR studies assessing the impact of GH deficiency on the heart [26,27,34]. Using CMR, Thomas et al. [27] studied the effects of GHD on myocardial structure and function and found that AoGHD patients have reduced aortic area and LV Mass index (Mi) compared to age- and sex matched healthy controls, but both these cardiac indexes increased after 1 year of GH treatment.

Typically, adults with GHD have an adverse lipid profile [28]. In particular, increased low-density lipoprotein (LDL) cholesterol and triglycerides have been documented in both sexes, whereas decreased high-density lipoprotein (HDL) cholesterol has been showed only in women, although the increased total cholesterol/HDL ratio occurred both in men and women [28]. Of interest, the severity and duration of GHD is correlated with the adverse lipid profile, with an inverse association emerging between IGF-I and LDL-cholesterol levels [2,3]. Contrariwise, no differences in lipoprotein (a) and apolipoprotein B levels were found between GHD and controls [28,29]. Other cardiovascular risk factors, including increased homocysteine and C-reactive protein levels (CRP) are present in GHD patients [29]. In particular, GHD patients have an approximately 4- to 5-fold increase in CRP [29,30], suggesting the presence of a pro-inflammatory state related to GHD [31,32]. Also, other pro-inflammatory factors may be involved in pathophysiological mechanisms of GHD-related cardiovascular complications. Among them, interleukin (IL-6) and tumor necrosis factor (TNF)- $\alpha$  are well known to play a major role in causing endothelial dysfunction [32]. Increased IL-6 and TNF- $\alpha$  levels have been documented in patients with GHD, independently of BMI or obesity [29]. Recently, it has been observed that GHD is associated with altered adipokine protein expression pattern and increased adipocyte diameter, which may predispose white adipose tissue to hypoxia and adipocyte dysfunction, paving the way to the development of the low-grade chronic inflammation [29,33,34]. Conflicting data are available in the literature on leptin levels in GHD patients, and some studies found that its levels were higher in GHD patients than in controls [35–37], while others did not [38]. One study in humans also failed to detect any effect of GH on circulating leptin concentrations [39]. Pregnancy-associated plasma

protein-A (PAPP-A) was found to be elevated in GHD patients [40]. This may be of particular interest, since PAPP-A is both a cardiovascular risk factor and a mediator of IGF-I bioavailability [40].

GHD is associated with changes in body composition, including reduced lean body mass and increased visceral adiposity [41,42], a phenotype that has been closely linked to insulin resistance and glucose intolerance. Insulin resistance, determined by a decreased insulin-stimulated glucose uptake by fat and skeletal muscle, is an important feature of the metabolic syndrome (MetS) and is associated with low-grade chronic inflammation, endothelial dysfunction and increased cardiovascular mortality [43]. Low, normal and high basal insulin levels have been found in GHD adults, being the degree of obesity a possible confounding factor [14]. In contrast to patients affected by MetS, significantly elevated insulin levels might be not characteristically observed in patients with GHD. However, using the hyperinsulinemic euglycemic clamp method, Johansson et al. [44] showed a 2–3-fold reduction in insulin sensitivity in GHD patients compared with controls, despite normal fasting glucose and insulin levels. As so far, the prevalence of MetS is increased in GHD patients. van der Klaauw et al. [45] documented that GHD patients had a more than 2-fold higher prevalence of MetS when compared with the general population. Also, Attanasio et al. [46] found that MetS prevalence was increased in GHD patients. Interestingly, lean individuals with GHD have larger waist circumference and more abdominal adiposity, with a proportional increase in subcutaneous and visceral tissue with respect to control subjects [33]. Among all these indirect cardiovascular risk factors, abdominal obesity, assessed simply by waist circumference or waist:hip ratio is a well-known negative predictor of subsequent coronary artery disease [47]. Patients with GHD were consistently proven to be affected with centrally distributed adiposity and, additionally, with dyslipidaemia [2–4], the treatment of which becomes crucial in primary and secondary prevention of cardiovascular disease.

Conflicting results have reported in the literature regarding blood pressure (BP) and peripheral resistance in GHD. On the one side, some studies reported slight increases in BP in GHD patients [2–4,48]. The association between GHD and altered BP was confirmed by a large study, which mainly consisted of AoGHD patients without recombinant human rhGH replacement treatment [48]. Similarly, an observational study recruiting almost 1000 GHD patients reported an increased prevalence of hypertension compared to the general population (22% vs.15%) [49]. Consequently, GHD was found to be associated with an increased activity of the sympathetic nervous system, with a diastolic BP around 10 mmHg higher in GHD patients than in controls [50]. On the other side, unaltered BP profiles were also reported [51], while BP was even reported to be reduced in young GHD adults [2–4,52]. Likewise, a study from our group failed to document any increase in the prevalence of hypertension in 56 patients classified to have severe GHD compared to sex- and age-matched healthy controls, while showing a decreased systolic BP at peak physical exercise [17]. While circadian BP patterns have been reported to be modified in adult GHD patients [53], a study on 24-h ambulatory BP and circadian rhythm found significant decreases in both systolic and diastolic BP in adult GHD subjects, without any change in circadian rhythm [54].

Conversely, GHD has been consistently found to be associated with vascular endothelial dysfunction and premature vascular atherosclerosis. A decreased formation of NO is reported to occur in untreated GHD patients [55] and, because NO plays a key role in regulating endothelial function and in inhibiting muscle cell proliferation, it is reasonable to hypothesize that a reduced NO synthesis might be implicated in the endothelial dysfunction of patients with GHD. In fact, patients with GHD were shown to have increased carotid intima-media thickness (IMT), one of the earliest morphological changes in the arterial wall in the process of atherogenesis. Markussis et al. firstly showed increased carotid IMT and higher prevalence of atheromatous plaque of common carotid artery in otherwise asymptomatic GHD patients [51]. Afterwards, the association between GHD and increased carotid IMT and/or atherosclerotic plaques, as well as vascular endothelial dysfunction, was confirmed in other series of GHD patients, although with some discrepancies among data [2,3,55,57], likely related to the variability of IGF-I levels in GHD patients. Indeed, it has been found that only patients with IGF-I levels below the normal range presented an increased IMT value and well-defined atherosclerotic plaques at the level of common carotid arteries [2,3]. Although the relationship between premature atherosclerosis and GH and/or IGF-1 deficiency is still far to be completely elucidated, it can be postulated that the presence of IGF-I deficiency *per se* is associated with increased IMT and atherosclerotic plaques at the level of the carotid arteries. As further findings, a number of different markers of vascular and

endothelial dysfunction [58,59] are reportedly altered in GHD patients, including less distensibility of the aorta and impaired vasodilatory flow [60], disorders in the coagulation and fibrinolytic system components, and abnormalities in inflammatory cardiovascular markers, suggestive of a prothrombotic diathesis [2–4,29]. Notably, some of these abnormalities, mainly hyperfibrinogenemia, fibrinolytic markers, soluble adhesion molecules, and other inflammatory cytokines were more predominant in AoGHD than in CoGHD. Although there is scant evidence on a direct association with the disease severity [2,3,61], these alterations might contribute to the increased prevalence of cardiovascular diseases associated with GHD and could be considered the possible link between GHD, inflammation, and atherosclerosis [29,40].

### Effects of rhGH replacement therapy on cardiovascular risk factors and system in adult patients

In spite of existing controversies on cardiovascular impairment of GHD patients, an overall agreement exists in the literature on the ability of GH replacement therapy to improve most cardiovascular risk factors outlined in adult hypopituitary patients [2–4,29]. However, optimal GH dosing and modality of treatment are warranted to maximize the benefits of GH therapy and minimize its potential risks [62].

Robust evidence supports the effectiveness of long-term GH replacement to improve the body composition. GH replacement produces a gradual increase of lean body mass by 2–5 kg and a reduction in fat mass by 30% (approximately 4–6 kg of visceral fat) [63]. The gain in lean body mass is maintained for at least 10 years of GH replacement both in men and women, although the time necessary to detect significant changes may differ between genders. In fact, both men and women lose most of their fat mass in the first year of GH replacement, but men maintained their body weight unaltered over the next nine years of observation, while women regained fat mass during the subsequent two years, after which fat mass remained unchanged until ten years of therapy [64]. Interestingly, changes in body composition appeared to be at least in part sustained after 15 years of therapy [65].

According to the Framingham model, the improvement in body composition reflects a 3–4% decrease in the incidence of coronary heart disease over ten years; thus, this effect of GH replacement therapy represents *per se* the single most important factor in reducing vascular risk [65].

Nevertheless, it has been suggested that dyslipidaemia is the strongest contributor of the excess in cardiovascular risk associated with hypopituitarism [28,29]. Abnormalities in serum lipid concentrations improved with GH replacement therapy, and the same applies to impairment in fibrinolysis [62]. A meta-analysis of blinded, randomized, placebo-controlled trials using low doses and long-duration GH treatment showed that GH replacement has beneficial effects on body composition, total and LDL cholesterol levels, as well as diastolic blood pressure, without significant effects on triglycerides levels [23]. While the positive effect of GH therapy on lipid profile was confirmed in a long-term 15-year prospective study [65], another 7-year study failed to evidence this beneficial effect [66]. In addition to benefits on serum cholesterol level, GH replacement was shown to improve apolipoprotein B levels in one study [67], while lipoprotein (a) levels increased during GH treatment in others [67,68]. Nevertheless, these unfavorable changes may be outweighed by the beneficial effects of GH replacement on total cholesterol and LDL-C levels. Additional benefits on serum lipid levels may be achieved by combination therapy with GH and statin treatment, and data from KIMS survey suggest that the effect of the concomitant treatments is additive [69].

Globally considering the effects on body composition and lipid profile, a number of studies confirm that long-term treatment with GH improves the constellation of metabolic parameters of MetS [45,46,70–74]. On the other hand, the effects by GH replacement on insulin sensitivity are still debated [75,76]. This controversy might be partially explained by differences in the duration of treatment among the studies, as GH replacement seems to further deteriorate insulin sensitivity in the short-term, namely after 6 weeks; conversely, longer courses of GH treatment were proven to return insulin sensitivity to baseline values through the increase in IGF-1 levels and the reduction of fat body mass [2–4]. Accordingly, in a long-term trial, seven-year GH replacement provided protection from the age-related decline in insulin sensitivity [77]. Among emerging cardiovascular risk factors, it has also been reported that GH replacement can improve low-grade inflammation, as documented by a reduction in

CRP [29,34], TNF- $\alpha$  [78], and IL-6 [34], well characterized inflammatory markers of atherosclerosis. Some positive effects of GH replacement can also be observed for adipokines like adiponectin, leptin [35,36], and pregnancy-associated plasma protein A (PAPP-A), a specific protease whose substrate is IGF-I, which is considered as a biological marker of unstable atherosclerotic plaques [29]. In line with previous studies [79,80], GH replacement exerts positive effects on the sympatho-vagal balance, endothelial function and blood pressure levels in GHD patients, which might contribute to improve their atherosclerotic profile.

In several series of adult GHD patients, GH replacement for 6–24 months was associated with improved IMT at common carotid arteries, reaching levels recorded in controls [2–4,16,56,57], while withdrawal of GH replacement for 6 months in severe GHD adults, but not in adolescents [2,3], was associated with an increase in IMT and further impairment of the cardiovascular risk [16]. Moreover, GH replacement induces a significant increase in flow-mediated dilation, a marker of endothelial function and arterial compliance [2,3]. Cardiac mass is another target of HG therapy and an increase in LV mass is commonly documented in the early phase of GH replacement therapy of GHD adults [2–4,2–4,81,82] as well as children [2,3,83–85]. Amato et al. [83] first showed that GH replacement induced a 26% increase in the LVMi and a 12% increase in the LVEF, which disappeared six months after GH discontinuation. In addition, Ter Maaten et al. [86] found that the hypertrophic effect of GH replacement was short-lasting also during the treatment, as LV mass returned to normal after two years, and similar to pretreatment values after ten-year replacement. In seven adults with AoGHD, 42 months of open GH treatment increased the LV mass and decreased the atrial emptying index, which reflects diastolic function, as compared with healthy matched controls [87].

These results suggest also that patients' age might *per se* promote inappropriate increments in LV mass during long-term GH replacement. However, it should be noted that the doses of GH replacement in these studies were higher than that used currently. In effect, the dose employed during the last decade was reduced from 20 to 26  $\mu\text{g}/\text{kg}$  bodyweight in the initial studies to 4–6  $\mu\text{g}/\text{kg}$  bodyweight in modern ones.

Together, studies so far published seem to imply that the beneficial effects of current low-dose GH regimens may be counterbalanced by potentially harmful effects of initially-used high GH dose, whereas low-dose individualized GH replacement is effective in improving cardiac function and carries a lower risk of developing cardiac hypertrophy in the long-term [2–4]. However, if an inappropriately high dose of GH is given, there is a risk of an unwanted increment in left ventricular mass, particularly in elderly GHD patients during long-term treatment [2–4].

A few studies did not report any significant change in cardiac mass and performance [2–4]. Contrariwise, we observed a significant increase of the LVEF at peak exercise after 12 month of GH replacement in a cohort of young GHD patients, even if exercise-induced changes of LVEF remained significantly lower than controls after treatment [2,3].

Compared to GHD patients who refused GH replacement, only patients receiving GH replacement showed an improvement of cardiovascular risk parameters, cardiac mass and function parameters after 12 months [2,3]. It should be emphasized, however, that GH replacement, for 12 months is unable to completely normalize cardiac performance, thus indicating that cardiac performance should be monitored in long-term studies. In fact, Chrisoulidou et al. [66] reported a decrease of diastolic blood pressure and an improvement of diastolic filling persisting seven years after GH replacement.

## Summary

GH replacement increases cardiac size, not exceeding normal values, improves cardiac performance, more evidently on peak exercise, affects positively body composition and lipid profile, and reduces IMT at common carotid arteries. Despite this large body of evidence on the beneficial effects of GH replacement in GHD patients, however, the most recent interventional studies failed to consistently show GH-mediated improvements in cardiac and prognostic outcomes [88–92]. To weight the beneficial effect of GH replacement in terms of reduced mortality is a relevant clinical issue. Currently, there is no abundance of data regarding the effect of GH replacement on cardiovascular morbidity and mortality [2–4,13,93]. Recently, Gazzaruso et al. [29] underpinned the lack of reliable risk markers in order to attain therapeutic benefit as much as possible by GH replacement, so confirming that more

accurate prognostic markers have to be identified yet. Furthermore, De Gregorio et al. [94] underlined that hypertension and age are important components of the natural history of GHD and suggested that GH replacement optimization and close follow-up of patients with GHD could reduce the cumulative CV event rates. However, the results of a large registry database showed that GH replacement may be important in adult GHD not only to improve general health and wellbeing, but also to reduce the risk of premature mortality [95]. As the individual changes in the cardiovascular risk factors in all the studies are small and affected by several confounding factors, the global benefit of GH replacement on cardiovascular mortality remains to be determined.

### Practice points

- GHD affects heart and the vasculature.
- The role for conventional CV risk factors has not been well established.
- GHD is associated with a number of detrimental factors that affect the cardiovascular system.
- GH replacement improves cardiac size, not exceeding normal values, and cardiac performance.
- Optimizing GH therapy is mandatory to prevent side effects.

### Research agenda

- Studies are required to identify accurate prognosticators of cardiovascular risk.
- Studies are required to evaluate whether new imaging techniques have concrete advantages for the assessment of cardiovascular system in clinical practice.
- Further prospective and long-term studies are guaranteed to evaluate the effective reduction of cardiovascular mortality.

### Conflict of interest statement

The authors have nothing to disclose.

### References

- [1] Colao A, Feron D, Marzullo P, et al. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. *Endocr Rev* 2004;25:102–52.
- \*[2] Colao A, Di Somma C, Savanelli MC, et al. Beginning to end: cardiovascular implications of growth hormone (GH) deficiency and GH therapy. *Growth Hormone IGF Res* 2006;16:S41–8.
- \*[3] Colao A. The GH-IGF-I axis and the cardiovascular system: clinical implications. *Clin Endocrinol* 2008;69(3):347–58.
- \*[4] Isgaard J, Arcopinto M, Karason K, et al. GH and the cardiovascular system: an update on a topic at heart. *Endocrine* 2015; 48(1):25–35.
- [5] Arcopinto M, Bobbio E, Bossone E, et al. The GH/IGF-1 axis in chronic heart failure. *Endocrine* 2015;48(1):25–35.
- [6] Delafontaine P. Insulin-like growth factor I and its binding proteins in the cardiovascular system. *Cardiovasc Res* 1995;30: 825–34.
- [7] D'Ercole AJ, Stiles AD, Underwood LE. Tissue concentrations of somatomedin C: further evidence for multiple sites of synthesis and paracrine or autocrine mechanisms of action. *Proc Natl Acad Sci USA* 1984;81:935–9.
- [8] Ito H, Hiroe M, Hirata Y, et al. Insulin-like growth factor-I induces hypertrophy with enhanced expression of muscle specific genes in cultured rat cardiomyocytes. *Circulation* 1993;87:1715–21.
- [9] DeBosch B, Treskov I, Lupu TS, et al. Akt1 is required for physiological cardiac growth. *Circulation* 2006;113:2097–104.
- [10] Chen DB, Wang L, Wang PH. Insulin-like growth factor I retards apoptotic signaling induced by ethanol in cardiomyocytes. *Life Sci* 2000;67:1683–93.
- [11] Cittadini A, Ishiguro Y, Strömer H, et al. Insulin like growth factor-1 but not growth hormone augments mammalian myocardial contractility by sensitizing the myofilament to  $Ca^{2+}$  through a wortmannin-sensitive pathway: studies in rat and ferret isolated muscles. *Circulation Res* 1998;83:50–9.

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- [12] Standley PR, Zhang F, Zayas RM, et al. IGF-I regulation of Na(+)-K(+)-ATPase in rat arterial smooth muscle. *Am J Physiol* 1997;273:E113–21.
- \*[13] Sherlock M, Ayuk J, Tomlinson JW, et al. Mortality in patients with pituitary disease. *Endocr Rev* 2010;31(3):301–42.
- \*[14] McCallum RW, Petrie JR, Dominiczak AF, et al. Growth hormone deficiency and vascular risk. *Clin Endocrinol* 2002;57:11–24.
- [15] Beznak M. The restoration of cardiac hypertrophy and blood pressure in hypophysectomized rats by large doses of lyophilized anterior pituitary and growth hormone. *J Physiol* 1954;124:64–7.
- [16] Colao A, Cuocolo A, Di Somma C, et al. Does the age of onset of growth hormone deficiency affect cardiac performance? A radionuclide angiography study. *Clin Endocrinol* 2000;52:447–55.
- [17] Colao A, Di Somma C, Cuocolo A, et al. The severity of growth hormone deficiency correlates with the severity of cardiac impairment in 100 adult patients with hypopituitarism: an observational, case-control study. *J Clin Endocrinol Metab* 2004;89:5908–6004.
- [18] Boschetti M, Agosti S, Albanese V, et al. One year GH replacement therapy reduces early cardiac TOD (Target Organ Damage) in adult GHD patients. *Endocrine* 2017;55(2):573–81.
- [19] Marwick TH, Leano RL, Brown J, et al. Myocardial strain measurement with 2-dimensional speckle-tracking echocardiography: definition of normal range. *JACC Cardiovasc Imaging* 2009;2:80–4.
- [20] Nishikage T, Nakai H, Lang RM, et al. Subclinical left ventricular longitudinal systolic dysfunction in hypertension with no evidence of heart failure. *Circ J* 2008;72:189–94.
- [21] Nakai H, Takeuchi M, Nishikage T, et al. Subclinical left ventricular dysfunction in asymptomatic diabetic patients assessed by two-dimensional speckle-tracking echocardiography: correlation with diabetic duration. *Eur J Echocardiogr* 2009;10:926–32.
- [22] Mihaila S, Mincu RI, Rimbas RC, et al. Growth hormone deficiency in adults impacts left ventricular mechanics: a two-dimensional speckle-tracking study. *Can J Cardiol* 2015;31(6):752–9.
- [23] Maisson P, Chanson P. Cardiac effects of growth hormone in adults with growth hormone deficiency: a meta-analysis. *Circulation* 2003;108(21):2648–52.
- [24] Gutmark-Little I, Backeljauw PF. Cardiac magnetic resonance imaging in Turner syndrome. *Clin Endocrinol* 2013;78(5):646–58.
- [25] Maron MS. Clinical utility of cardiovascular magnetic resonance in hypertrophic cardiomyopathy. *J Cardiovasc Magnetic Reson* 2012;14:13.
- [26] Andreassen M, Faber J, Kjaer A, et al. Cardiac function in growth hormone deficient patients before and after 1 year with replacement therapy: a magnetic resonance imaging study. *Pituitary* 2014;14(1):1–10.
- [27] Thomas JD, Dattani A, Zemrak F, et al. Characterisation of myocardial structure and function in adult-onset growth hormone deficiency using cardiac magnetic resonance. *Endocrine* 2016;54(3):778–87.
- [28] Abdu TA, Neary R, Elhadd TA, et al. Coronary risk in growth hormone deficient hypopituitary adults: increased predicted risk is due largely to lipid profile abnormalities. *Clin Endocrinol* 2001;55(2):209–16.
- \*[29] Gazzaruso M, Gola I, Karamouzis R, et al. Cardiovascular risk in adult patients with growth hormone (GH) deficiency and following substitution with GH—an update. *J Clin Endocrinol Metab* 2014;99(1):18–29.
- [30] McCallum RW, Sainsbury CA, Spiers A, et al. Growth hormone replacement reduces C-reactive protein and large-artery stiffness but does not alter endothelial function in patients with adult growth hormone deficiency. *Clin Endocrinol* 2005;62(4):473–9.
- [31] Lee SD, Huang CY, Shu WT, et al. Pro-inflammatory states and IGF-I level in ischemic heart disease with low or high serum iron. *Clin chimica Acta Int J Clin Chem* 2006;370(1–2):50–6.
- [32] Libby P. Inflammation in atherosclerosis. *Arteriosclerosis Thromb Vasc Biol* 2012;32(9):2045–51.
- [33] Ukropec J, Penesová A, Skopková M, et al. Adipokine protein expression pattern in growth hormone deficiency predisposes to the increased fat cell size and the whole body metabolic derangements. *J Clin Endocrinol Metab* 2008;93(6):2255–62.
- [34] Bollerslev J, Ueland T, Jørgensen AP, et al. Positive effects of a physiological dose of GH on markers of atherogenesis: a placebo controlled study in patients with adult-onset GH deficiency. *Eur J Endocrinol* 2006;154(4):537–43.
- [35] Miyakawa M, Tsushima T, Murakami H, et al. Effect of growth hormone (GH) on serum concentrations of leptin: study in patients with acromegaly and GH deficiency. *J Clin Endocrinol Metab* 1998;83(10):3476–9.
- [36] Giavoli C, Cappiello V, Corbetta S, et al. Different effects of short and long-term recombinant hGH administration on ghrelin and adiponectin levels in GH-deficient adults. *Clin Endocrinol* 2004;61(1):81–7.
- [37] Fisker S, Vahl N, Hansen TB, et al. Serum leptin is increased in growth hormone deficient adults: relationship to body composition and effects of placebo-controlled growth hormone therapy for 1 year. *Metabolism* 1997;46(7):812–7.
- [38] Florkowski CM, Collier GR, Zimmet PZ, et al. Low-dose growth hormone replacement lowers plasma leptin and fat stores without affecting body mass index in adults with growth hormone deficiency. *Clin Endocrinol* 1996;45(6):769–73.
- [39] Berneis K, Vosmeer S, Keller U. Effects of glucocorticoids and of growth hormone on serum leptin concentrations in man. *Eur J Endocrinol* 1996;135(6):663–5.
- [40] Li L, Ren W, Li J. Increase in serum pregnancy-associated plasma protein-A is correlated with increase in cardiovascular risk factors in adult patients with growth hormone deficiency. *Endocrine* 2012;42(2):375–81.
- [41] Attallah H, Friedlander AL, Hoffman AR. Visceral obesity, impaired glucose tolerance, metabolic syndrome, and growth hormone therapy. *Growth Hormone IGF Res* 2006;16:S62–7.
- [42] Savastano S, Di Somma C, Barrea L, et al. The complex relationship between obesity and the somatotropic axis: the long and winding road. *Growth Hormone IGF Res* 2014;24(6):221.
- [43] Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1988;37:1595–607.
- [44] Johansson JO, Fowelin J, Landbin K, et al. Growth hormone-deficient adults are insulin-resistant. *Metab Clin Exp* 1995;44:1126–9.
- [45] van der Klaauw AA, Biermasz NR, Feskens EJ, et al. The prevalence of the metabolic syndrome is increased in patients with GH deficiency, irrespective of long-term substitution with recombinant human GH. *Eur J Endocrinol* 2007;156(4):455–62.



- [46] Attanasio AF, Mo D, Erfurth EM, et al. Prevalence of metabolic syndrome in adult hypopituitary growth hormone (GH)-deficient patients before and after GH replacement. *J Clin Endocrinol Metab* 2010;95(1):74–81.
- [47] Ohlson LO, Larsson B, Svardssudd K, et al. The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes* 1985;34:1055–8.
- [48] Rosen T, Eden S, Larson G, et al. Cardiovascular risk factors in adult patients with growth hormone deficiency. *Acta Endocrinol* 1993;129:195–200.
- [49] Sanmarti A, Lucas A, Hawkins F, et al. Observational study in adult hypopituitary patients with untreated growth hormone deficiency (ODA study). Socioeconomic impact and health status. *Eur J Endocrinol* 1999;141:481–9.
- [50] Sverrisdottir YB, Elam M, Herlitz H, et al. Intense sympathetic nerve activity in adults with hypopituitarism and untreated growth hormone deficiency. *J Clin Endocrinol Metab* 1998;83:1881–5.
- [51] Markkussis V, Beshyah S, Fisher C, et al. Detection of premature atherosclerosis by high-resolution ultrasonography in symptom-free hypopituitary adults. *Lancet* 1992;340:1188–92.
- [52] Cittadini A, Cuocolo A, Merola B, et al. Impaired cardiac performance in GH-deficient adults and its improvement after GH replacement. *Am J Physiol* 1994;267:E219–25.
- [53] Conceição FL, de RooijMansur VA, Brasil RR, et al. Ambulatory monitoring of blood pressure in growth hormone-deficient adults. *Blood Press Monit* 2002;7:89–94.
- [54] Ahmad AM, Hopkins MT, Weston PJ, et al. Effects of GH replacement on 24-h ambulatory blood pressure and its circadian rhythm in adult GH deficiency. *Clin Endocrinol* 2002;56:431–7.
- [55] Böger RH, Skamira C, Bode-Böger SM, et al. Nitric oxide mediates the hemodynamic effects of recombinant growth hormone in patients with acquired growth hormone deficiency. *J Clin Invest* 1996;98:2706–13.
- [56] Borson-Chazot F, Serusclat A, Kalfallah Y, et al. Decrease in carotid intima-media thickness after 1 year growth hormone (GH) treatment in adults with GH deficiency. *J Clin Endocrinol Metab* 1999;84:1329–33.
- [57] Pfeifer M, Verhovec R, Zizek B, et al. Growth hormone (GH) treatment reverses early atherosclerotic changes in GH-deficient adults. *J Clin Endocrinol Metab* 1999;84:453–7.
- [58] Evans LM, Davies JS, Goodfellow J, et al. Endothelial dysfunction in hypopituitary adults with growth hormone deficiency. *Clin Endocrinol* 1999;50:457–64.
- [59] Lanes R, Soros A, Flores K, et al. Endothelial function, carotid artery intima-media thickness, epicardial adipose tissue, and left ventricular mass and function in growth hormone-deficient adolescents: apparent effects of growth hormone treatment on these parameters. *J Clin Endocrinol Metab* 2005;90:3978–82.
- [60] Lehmann ED, Hopkins KD, Weissberger AJ, et al. Aortic distensibility in growth hormone deficient adults. *Lancet* 1993;341(8840):309.
- \*[61] Carrol PV, Christ ER. Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. *J Clin Endocrinol Metab* 1998;83:382–95.
- \*[62] Drake W, Howell S, Monson J, et al. Optimizing GH therapy in adults and children. *Endocr Rev* 2001;22:425–50.
- [63] Bengtsson BA, Eden S, Lonn L, et al. Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. *J Clin Endocrinol Metab* 1993;76:309–17.
- \*[64] Gotherstrom G, Bengtsson BA, Bosaeus I, et al. A 10-year prospective study of the metabolic effects of growth hormone replacement in adults. *J Clin Endocrinol Metab* 2007;92:1442–5.
- \*[65] Elbornsson M, Götherström G, Bosaeus I, et al. Fifteen years of growth hormone replacement improves body composition and cardiovascular risk factors. *Eur J Endocrinol* 2013;168:745–53.
- [66] Chrisoulidou A, Beshyah SA, Rutherford O, et al. Effects of 7 years of growth hormone replacement therapy in hypopituitary adults. *J Clin Endocrinol Metab* 2000;85(10):3762–9.
- [67] Weaver JU, Monson JP, Noonan K, et al. The effect of low dose recombinant human growth hormone replacement on regional fat distribution, insulin sensitivity, and cardiovascular risk factors in hypopituitary adults. *J Clin Endocrinol Metab* 1995;80:153–9.
- [68] Nolte W, Radisch C, Armstrong VW, et al. The effect of recombinant human GH replacement therapy on lipoprotein(a) and other lipid parameters in adults with acquired GH deficiency: results of a double-blind and placebo-controlled trial. *Eur J Endocrinol* 1997;137:459–66.
- [69] Monson JP, Jönsson P, Koltowska-Hägström M, et al. Growth hormone (GH) replacement decreases serum total and LDL cholesterol in hypopituitary patients on maintenance HMG CoA reductase inhibitor (statin) therapy. *Clin Endocrinol* 2007;67(4):623–8.
- [70] Cenci MC, Conceição FL, Soares DV, et al. Impact of 5 years of growth hormone replacement therapy on cardiovascular risk factors in growth hormone-deficient adults. *MetabClin Exp* 2008;57(1):121–9.
- [71] Roemmler J, Kuenkler M, Schneider HJ, et al. Comparison of glucose and lipid metabolism and bone mineralization in patients with growth hormone deficiency with and without long-term growth hormone replacement. *MetabClin Exp* 2010;59(3):350–8.
- [72] Oliveira CR, Salvatori R, Barreto-Filho JA, et al. Insulin sensitivity and  $\beta$ -cell function in adults with lifetime, untreated isolated growth hormone deficiency. *J Clin Endocrinol Metab* 2012;97(3):1013–9.
- [73] Beauregard C, Utz AL, Schaub AE, et al. Growth hormone decreases visceral fat and improves cardiovascular risk markers in women with hypopituitarism: a randomized, placebo-controlled study. *J Clin Endocrinol Metab* 2008;93(6):2063–71.
- [74] Arafat AM, Möhlig M, Weickert MO, et al. Improved insulin sensitivity, preserved beta cell function and improved whole-body glucose metabolism after low-dose growth hormone replacement therapy in adults with severe growth hormone deficiency: a pilot study. *Diabetologia* 2010;53(7):1304–13.
- [75] Christopher M, Hew F, Oakley M, et al. Defects of insulin action and skeletal muscle glucose metabolism in growth hormone-deficient adults persist after 24 months of recombinant human growth hormone therapy. *J Clin Endocrinol Metab* 1998;83:1668–81.
- [76] Svensson J, Fowelin J, Landin K, et al. Effects of 7 years of GH-replacement therapy on insulin sensitivity in GH-deficient adults. *J Clin Endocrinol Metab* 2002;87:2121–7.
- [77] Fowelin J, Attvall S, Lager I, et al. Effects of treatment with recombinant human growth hormone on insulin sensitivity and glucose metabolism in adults with hormone deficiency. *MetabClin Exp* 1993;42:1443–7.

- [78] Andiran N, Yordam N. TNF-alpha levels in children with growth hormone deficiency and the effect of long-term growth hormone replacement therapy. *Growth Hormone IGF Res* 2007;17(2):149–53.
- [79] Sverrisdottir Y, Elam M, Caidahl K, et al. The effect of growth hormone (GH) replacement therapy on sympathetic nerve hyperactivity in hypopituitary adults: a double-blind, placebo-controlled, crossover, short-term trial followed by long-term open GH replacement in hypopituitary adults. *J Hypertens* 2003;10:1905–14.
- [80] Boschetti M, Casu M, Moretti S, et al. Autonomic nervous system and cardiovascular risk assessment during one year of growth hormone replacement therapy in adults with growth hormone deficiency. *Horm (Athens, Greece)* 2015;14:134–41.
- [81] Cuneo RC, Salomon F, Wilmshurst P, et al. Cardiovascular effects of growth hormone treatment in growth-hormone-deficient adults: stimulation of the renin–aldosterone system. *Clin Sci* 1991;81:587–92.
- [82] Beshyah SA, Shahi M, Foale R, et al. Cardiovascular effects of prolonged growth hormone replacement in adults. *J Intern Med* 1995;237:35–42.
- [83] Amato G, Carella C, Fazio S, et al. Body composition, bone metabolism, and heart structure and function in growth hormone (GH)-deficient adults before and after GH replacement therapy at low doses. *J Clin Endocrinol Metab* 1993;77:1671–6.
- [84] Shulman DI, Root AW, Diamond FB, et al. Effects of one year of recombinant human growth hormone (GH) therapy on cardiac mass and function in children with classical GH deficiency. *J Clin Metab* 2003;88:4095–9.
- [85] Salerno M, Esposito V, Spinelli L, et al. Left ventricular mass and function in children with GH deficiency before and during 12 months GH replacement therapy. *Clin Endocrinol* 2004;60:630–6.
- [86] TerMaaten J, De Boer H, Kamp O, et al. Long-term effects of growth hormone (GH) replacement in men with childhood-onset GH deficiency. *J Clin Endocrinol Metab* 1999;84(7):2373–80.
- [87] Johannsson G, Bengtsson BA, Andersson B, et al. Long-term cardiovascular effects of growth hormone treatment in GH-deficient adults. Preliminary data in a small group of patients. *Clin Endocrinol* 1996;45:305–14.
- [88] Gruson D, Alexopoulou O, Pasquet A, et al. Impact of growth hormone (GH) treatment on circulating Nt-proBNP concentrations and on cardiac function in adult GH-deficient patients. *Scand J Clin Lab Invest* 2012;72:387–94.
- [89] Cenci MC, Soares DV, Spina LD, et al. Comparison of two dose regimens of growth hormone (GH) with different target IGF-1 levels on glucose metabolism, lipid profile, cardiovascular function and anthropometric parameters in GH-deficient adults. *Growth Hormone IGF Res* 2012;22:116–21.
- [90] Newman CB, Frisch KA, Rosenzweig B, et al. Moderate doses of hGH (0.64 mg/d) improve lipids but not cardiovascular function in GH-deficient adults with normal baseline cardiac function. *J Clin Endocrinol Metab* 2011;96:122–32.
- [91] Cannavò S, Marini F, Curtò L, et al. High prevalence of coronary calcifications and increased risk for coronary heart disease in adults with growth hormone deficiency. *J Endocrinol Invest* 2011;34(1):32–7.
- [92] Schneider HJ, Klotsche J, Wittchen HU, et al. Effects of growth hormone replacement within the KIMS survey on estimated cardiovascular risk and predictors of risk reduction in patients with growth hormone deficiency. *Clin Endocrinol* 2011;75(6):825–30.
- [93] Hartman M, Xu R, Crowe BJ, et al. International HypoCCS Advisory Board: prospective safety surveillance of GH-deficient adults: comparison of GH-treated vs untreated patients. *J Clin Endocrinol Metab* 2013;98:980–8.
- [94] de Gregorio C, Andò G, Cannavò S, et al. Cardiovascular outcomes and conventional risk factors in non-diabetic adult patients with GH deficiency: a long-term retrospective cohort study. *Eur J Intern Med* 2015;26(10):813–8.
- [95] Abs R, Feldt-Rasmussen U, Mattsson AF, et al. Determinants of cardiovascular risk in 2589 hypopituitary GH-deficient adults – a KIMS database analysis. *Eur J Endocrinol* 2006;155:79–90.