Cardiovascular Risk in Adult Patients With Growth Hormone (GH) Deficiency and Following Substitution With GH—An Update

Carmine Gazzaruso, Monica Gola, Ioannis Karamouzis, Raffaele Giubbini, and Andrea Giustina

Chair of Endocrinology (I.K., A.G.) and Nuclear Medicine (R.G.), University of Brescia, 25123 Brescia, Italy; Department of Internal Medicine (C.G.), Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Donato, 20097 San Donato Milanese, Italy; and Department of Internal Medicine (M.G.), Mirandola Hospital, 41037 Modena, Italy

Context: GH deficiency (GHD) of the adult is a clinical condition characterized by the presence of several traditional and emerging cardiovascular risk factors that can significantly increase cardiovascular morbidity and mortality. It is still an open issue whether GH replacement is able not only to improve cardiovascular risk factors but also to decrease cardiovascular morbidity and mortality.

Evidence Acquisition: The major source of data acquisition included PubMed research strategies. Original articles, systematic reviews and meta-analyses, and included relevant citations were screened.

Evidence Synthesis: In untreated GHD, cardiovascular risk is increased due to abnormal lipid profile (increased total and low-density lipoprotein cholesterol, increased triglycerides, and reduced high-density lipoprotein cholesterol) and impaired glucose metabolism. Emerging cardiovascular risk factors/markers such as proinflammatory cytokines, C-reactive protein, and adipokines are also increased in GHD patients. Increased cardiovascular morbidity and mortality have also been reported in GHD. GH treatment has been shown to improve both traditional and emerging cardiovascular risk factors and markers. However, evidence on the effects of GH replacement on cardiovascular events and mortality is limited.

Conclusion: The GHD population may be considered at high cardiovascular risk, and GH substitution may be expected to bring an added value to patients with hypopituitarism in terms of cardiovascular protection. However, there is too limited evidence (rarely coming from randomized and controlled studies) to recommend GH treatment based on the cardiovascular status of the patients. **(*J Clin Endocrinol Metab* 99: 18–29, 2014)**

GH deficiency (GHD) of the adult is now recognized as a well-defined clinical condition, characterized by several signs and symptoms such as reduced quality of life (1–3) and physical fitness (4), osteopenia, osteoporosis (5–8), and increased cardiovascular risk (9), which are at least partially reversible by GH substitution (1–10). It is still an open issue whether GH replacement may be able not only to improve cardiovascular risk factors but also to decrease cardiovascular morbidity and mortality. The aim of this review was to update the current knowledge on the cardiovascular risk profile in adults with GHD with or without GH replacement. Traditional and emerging cardiovascular risk factors (Figure 1), as well as their impact on clinical endpoints, will be evaluated.

Traditional Cardiovascular Risk Factors in GHD Adults

Lipids

Adults with GHD often have significant changes in their lipid profile (11). Indeed, increased low-density li-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received May 30, 2013. Accepted October 7, 2013.
First Published Online November 11, 2013

Abbreviations: ADMA, asymmetrical dimethylarginine; BMI, body mass index; CRP, C-reactive protein; GHD, GH deficiency; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; MetS, metabolic syndrome; PAPP-A, pregnancy-associated plasma protein A; sdLDL, small dense LDL.

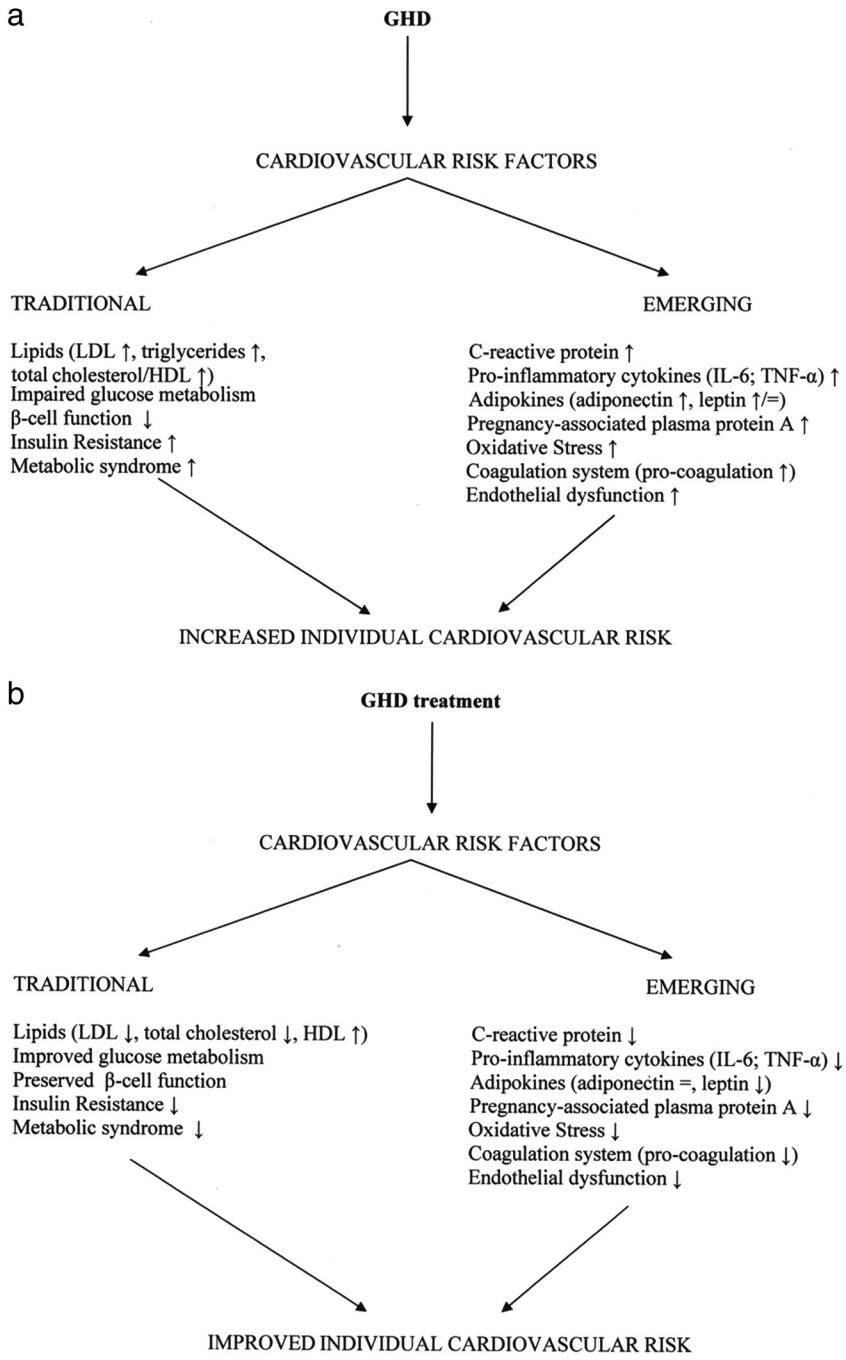

Figure 1. The potential impact of GHD (A) and GH replacement (B) on the individual cardiovascular risk.

poprotein (LDL) and triglycerides have been documented in both sexes, whereas decreased high-density lipoprotein (HDL) has been observed only in women; the elevated total cholesterol/HDL ratio regarded both men and women (11). No differences in additional risk factors, such as lipoprotein (a) (12, 13) and apolipoprotein B (14), were found between GHD and controls (11).

GH replacement was able to positively affect lipid profile in GHD patients: total cholesterol and LDL significantly decreased, whereas HDL increased (15–18) (Table 1). GH replacement may also decrease triglycerides (17). However, Florakis et al (19) showed that GH treatment was able to decrease total cholesterol and LDL and to slightly increase HDL, but no change was observed for triglycerides. A meta-analysis including 37 trials confirmed the positive effects of GH treatment on total and LDL cholesterol but did not find any effect on triglycerides (20). Also, in a recent long-term prospective study, 15 years of GH replacement reduced total cholesterol and LDL and increased HDL, but no significant variations were observed for triglycerides (21). Therefore, even if some studies did not find an improvement in lipid profile with long-term GH replacement (22, 23), it can be summarized that GHD adults have a high cardiovascular risk lipid profile at baseline and that in most of the studies, GH treatment tends to reverse to normal the total and LDL/HDL cholesterol levels.

Two other emerging issues deserve to be addressed. In fact, there is recent evidence that small dense LDL (sdLDL) may be independent cardiovascular risk factors (24). A small study by Rizzo et al (25) found that sdLDLs were common among patients with GHD and that GH replacement did not affect LDL size. Conversely, Salman et al (26) did not find any difference in sdLDLs between subjects with GHD and controls. The second issue is whether GH may have additive effects on 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) treatment. Interestingly, a synergistic, rather than additive, and proportional to baseline cholesterol value effect of this combination was reported (27). Therefore, in hypercholesterolemic GHD, clinicians should carefully balance relative risk/benefit profiles and eventually combine the two treatments.

Glucose metabolism and insulin resistance

Adult patients with GHD have increased visceral fat mass and often have an impaired glucose metabolism to-

Table 1. Summary of Studies of the Effects of GH Treatment on Lipid Profile

First Author (Ref.)	No. of patients	Mean GH Dose	Duration of Treatment, y	Outcome
Chrisoulidou (22)	12	0.7 mg/d	7	TC, LDL, HDL, and TG unchanged
Florakis (19)	24	0.3 mg/d	1.5	TC ↓, LDL ↓, HDL ↑, TG unchanged
Götherström (17)	118	Initially 0.98 mg/d, gradually titrated to 0.48 mg/d	5	TC ↓, LDL ↓, HDL ↑, TG ↓
Svensson (15)	11	Initially 1.1 mg/d, gradually titrated to 0.61 mg/d	7	LDL ↓, HDL ↑, TC and TG unchanged
Arwert (34)	23	Initially 0.97 mg/d, gradually titrated to 0.4 mg/d	10	TC ↓ (5th year), LDL ↓, HDL ↑, TG unchanged
van der Klaauw (16)	63	Initially 0.2 mg/d, gradually titrated to 0.5 mg/d	7	TC ↓, LDL ↓, HDL ↑, TG unchanged
Colson (18)	124	Initially 0.3 mg/d, gradually titrated to 0.5 mg/d	5	TC ↓, LDL ↓, HDL and TG unchanged
Monson (27)	61	0.32 mg/d	1	TC ↓, LDL ↓, HDL and TG unchanged
Götherström (53)	87	Initially 0.98 mg/d, gradually titrated to 0.47 mg/d	10	TC ↓, LDL ↓, HDL ↑, TG unchanged
Colao (54)	22	6 μg/kg·d	5	TC ↓, HDL ↑, TG ↓
Spielhagen (23)	81	Initially 0.29 mg/d, gradually titrated to 0.43 mg/d	10	TC and LDL unchanged
Elbornsson (21)	109	Initially 0.55 mg/d, gradually titrated to 0.4 mg/d	15	TC ↓, LDL ↓, HDL ↑, TG unchanged

TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; ↓ significant decrease; ↑ significant increase.

gether with insulin resistance (9, 10). The glycometabolic effects of GH therapy in GHD are conflicting. Indeed, some studies have documented an improvement in glucose metabolism and insulin sensitivity (15, 28, 29), but other investigations have observed no effect (30, 31) or at best a marginal effect (32–35). These conflicting data seem to be due to the duration of treatment. A short-term (up to 1 y) GH substitution seems to deteriorate glucose metabolism (32, 36, 37), whereas long-term treatment did not lead to significant variations in glucose and insulin metabolism (38); on the contrary, slightly lower fasting glucose levels were observed (39). In most of the long-term studies, an initial increase in glucose and insulin levels with an impairment of insulin sensitivity could be observed. This glycometabolic deterioration at the beginning of GH substitution may be caused by a decline of peripheral glucose utilization (40). After initial deterioration, glucose tolerance can improve, with glucose and insulin levels returning to baseline levels (15, 41). Insulin resistance could be exacerbated acutely by GH in GHD (42), whereas it has been shown that GH replacement decreasing visceral fat mass did not worsen insulin resistance (43). Moreover, low-dose 24- to 48-week GH treatment improved insulin sensitivity, preserved β-cell function, and improved glucose metabolism without affecting body composition or inducing lipolysis in a small group of six adults with severe GHD, likely via an increased IGF-1 bioavailability (44).

In synthesis, glycometabolic effects of GH substitution seem to be biphasic (mimicking what is observed for bone effects), leading initially to deterioration of an already altered glucose metabolism, but in the long-term, particularly with low-dose GH, an improvement of glucose handling is reported.

Metabolic syndrome (MetS)

The metabolic syndrome (MetS) is a cluster of risk factors (visceral obesity, impaired glucose metabolism, low HDL, high triglycerides, and hypertension) mainly associated with insulin resistance, inflammation, and endothelial dysfunction (45). MetS predicts the development of diabetes (41) and is strongly associated with cardiovascular diseases in the general population (45, 46) and in diabetic patients (47). The prevalence of MetS is increased in GHD patients (48). van der Klaauw et al (48) documented that GHD patients had a prevalence of MetS more than 2-fold higher when compared with the general population, mainly due to an increased prevalence of hypertension, abdominal obesity, and triglyceride levels. Also, Attanasio et al (49) found that MetS prevalence was increased in GHD patients. Interestingly, lean individuals with GHD had larger waist circumference and more abdominal adiposity with a proportional increase in sc and visceral tissue with respect to control subjects. Also, adipose tissue of obese GHD patients expressed many proinflammatory markers (50).

In a large study, waist circumference decreased after 1 and 2 years of GH treatment, respectively, but remained unchanged after 5 years of GH substitution when compared with baseline (51, 52). Götherström et al (53) observed that the reduction in body fat, after correction for age and sex, was sustained during 10-year GH treatment. In addition, there was a sustained improvement in serum lipid profile and glycated hemoglobin (53). The response to treatment of HDL and body composition were more marked in men, whereas women had more marked reduction in glycated hemoglobin (53). Other studies suggested that GH replacement did not affect the risk of type 2 diabetes in GHD with normal body mass index (BMI) (52). However, in severe GHD with increased prevalence of cardiovascular risk factors and surrogate markers of early atherosclerosis (intima-media thickness), 5-year GH replacement improved all metabolic parameters, reducing insulin resistance (54).

MetS is clinically an appropriate label for patients with GHD who do not often have a prominently altered cardiometabolic feature but show a cluster of mild alterations. There has been a long debate on MetS being an independent clinical entity (55, 56); in our opinion, GHD patients are often good examples of MetS clinical expressivity, and what could appear relatively modest changes in cardiometabolic parameters determined by GH substitution should be read in the context of a global improvement of MetS and of the added cardiovascular risk that MetS is bearing.

Traditional Cardiovascular Risk Factors During the Transition Period From Adolescence to Adulthood

Discontinuation of GH during the transition phase in GHD increased fat mass and diastolic blood pressure, with significant worsening in total and LDL cholesterol (57, 58). Beneficial effects on fat mass and LDL/HDL ratio of continuing GH replacement during the transition phase in childhood onset-GHD patients was also reported (59). Other authors, but not all (60, 61), showed a significant increase in fat mass also in partial GHD after GH discontinuation. Therefore, suspending GH during the transition period may cause unfavorable changes in cardiometabolic risk factors that may improve when GH treatment is resumed. No data are available for emerging cardiovascular risk factors in the GHD transition phase.

Emerging Cardiovascular Risk Factors

C-Reactive protein (CRP)

CRP is a marker of inflammation and is now considered an independent cardiovascular risk factor (62). Elevated CRP levels are associated with negative cardiovascular prognosis (62, 63) and can predict the development of type 2 diabetes (64, 65), hypertension (66), and MetS (67).

Both lean and obese subjects with GHD have an approximately 4- to 5-fold increase in CRP (50), suggesting a proinflammatory state linked directly to GHD (68, 69). Earlier studies had provided conflicting results on the effect of GH therapy on CRP. Bollerslev et al (70) showed that GH replacement was associated with reduced CRP, independently of weight or immune-modulating actions, even greater than that observed in a previous controlled study that enrolled only women (71). A significant negative correlation between CRP and IGF-1 at baseline and between the changes in CRP and IGF-1 after GH therapy was documented (71), whereas a decrease in body fat did not predict changes in CRP during GH treatment. Finally, Deepak et al (72) recently reported a significant GH-mediated reduction in CRP levels in GHD that was not affected by changes in body composition. Therefore, GHD is likely a proinflammatory state (see also below), and GH treatment may interrupt the vicious circle linking endocrine abnormality, inflammation, and atherosclerosis.

Proinflammatory cytokines

Several proinflammatory factors may be involved in pathophysiological mechanisms of GHD cardiovascular complications. Among them, IL-6 and TNF-α may have a major role in causing endothelial dysfunction (73, 74).

Increased IL-6 levels have been documented in patients with GHD independently of BMI or obesity; in addition, GH replacement was able to effectively reduce IL-6 production from monocytes (75). Bollerslev et al (70) showed that IL-6 was increased in GHD and that GH reduced IL-6 similarly to CRP in men.

Also, TNF-α was significantly higher in children with GHD than in controls; in addition, long-term GH therapy was able to effectively reduce its levels. These data suggested that GH could play an inhibitory role on TNF-α release in humans (76).

Adipokines

Adipose tissue produces a large variety of peptides with endocrine, paracrine, or autocrine actions called adipokines (72–74, 77, 78). The most abundant adipokine is adiponectin (72–74), which is decreased in obese patients, positively associated with insulin sensitivity, and inversely associated with the risk of type 2 diabetes (79, 80), exerting anti-inflammatory, antiatherogenic, and insulin-sensitizing effects (78, 79). Leptin is another important adipokine involved in the central control of energy homeostasis (77, 78); its activity is modulated by the soluble isoform of its receptor (78). Leptin is usually elevated

in obese subjects and can play an atherogenic, prothrombotic, and angiogenic role by stimulating vascular inflammation, oxidative stress, and smooth muscle hypertrophy (78).

Recently, it was observed that GHD was associated with an altered adipokine protein expression pattern and an increased adipocyte diameter: this may predispose the adipose tissue to hypoxia and chronic inflammation (50, 81). Conflicting data are available in the literature on leptin levels in GHD patients. Some studies found that levels were higher in GHD patients than in controls (81–84), but others did not (85). One study in humans also failed to detect any effect of GH on circulating leptin concentrations (86). In children with GHD, adiponectin and soluble leptin receptor levels were higher than in controls, whereas no differences in other adipokines were observed (87). A 12-month trial of GH replacement caused a decrease in leptin levels concomitantly with a restoration of normal IGF-1 concentrations (87). After 1 year GH also an increase in adiponectin levels was observed (83).

Pregnancy-associated plasma protein A (PAPP-A)

PAPP-A is a high-molecular-weight metalloproteinase produced by human artery vascular smooth muscle cells, which degrades IGF binding protein-4, increasing the levels of local unbound IGF-1 (88). PAPP-A is expressed in eroded and ruptured atherosclerotic plaques and has been proposed as a marker of increased risk of atherothrombotic events (88). Elevated PAPP-A levels were observed in acute coronary syndrome (89) and ischemic stroke (90).

PAPP-A levels were higher in GHD patients than in controls, and GH replacement lowered PAPP-A levels (91), which correlated positively with BMI and waist-hip ratio before and after treatment (91). Li et al (92) recently confirmed that in GHD patients, PAPP-A and CRP significantly increased with respect to matched controls without correlation between their levels. The study by Li et al suggested, but did not prove, that the rise of serum PAPP-A was a direct response to decreased systemic IGF-1 and hypothesized that PAPP-A could play a role in the development of atherosclerosis in GHD (10, 92).

These recent studies interestingly updated our knowledge on the interaction between GH and cytokines. In fact, they somewhat upgraded the role of the latter from simple markers of altered body composition and increased fat cell activity to a possible causative link between the lack of GH/IGF-1 and cardiovascular disease.

Oxidative stress

Oxidative stress seems to play a major role in the genesis and development of atherosclerosis (73, 74). The action of oxidative stress on atherosclerosis is mediated by lipid peroxidation, in particular of LDL (74).

Conflicting data are available on oxidative stress in patients with GHD. Smith et al (93) found that oxidative stress did not play a significant role in the proatherogenic state of patients with GHD, but González-Duarte et al (94) recently observed an important increase in oxidated LDL in these subjects. Some studies showed that short-term GH administration reduced lipid peroxidation in GHD (95, 96).

Coagulation system

Thrombosis plays a major role in the development of cardiovascular events due to an excess of procoagulative factors or impaired fibrinolysis (97). Therefore, coagulation abnormalities can be risk factors for cardiovascular morbidity and mortality (98). In patients with GHD, a reduced protein S activity that was normalized after GH replacement was recently documented (99). Data regarding the association between GHD and impaired fibrinolysis are conflicting. Some, but not all, studies found an impaired fibrinolytic activity (due to an excess of plasminogen activator inhibitor 1 and fibrinogen) that did improve after GH replacement (100–103).

Endothelial dysfunction

Endothelial dysfunction is crucial in the development of atherothrombosis and progression to cardiovascular diseases (104). Asymmetrical dimethylarginine (ADMA) is an endogenous inhibitor of endothelial nitric oxide synthase, an enzyme involved in correct endothelial function (105), considered a marker of endothelial dysfunction and potential risk factor for atherothrombosis (105). In GHD, an increase in ADMA was documented (106), and GH replacement reduced ADMA and improved endothelial function (107).

Cardiac function and morphology

Impaired cardiac functional reserve (108, 109) associated with chronotropic incompetence and impaired pressure-generating capacity was reported in severe GHD (110). Earlier investigations also documented reduced left ventricular (LV) mass, abnormalities in contractility and stroke volume index, reduced ejection fraction, and diastolic dysfunction (9, 111). A meta-analysis showed that GH replacement was associated with positive effects on LV mass, intraventricular septum, diastolic function, and stroke volume index, whereas no effects were observed on systolic parameters (9, 112). In a 5-year follow-up study, Cenci et al (113) documented a post-GH improvement in exercise capacity and maximum oxygen uptake. In addition, in that study LV mass increased progressively during

GH replacement, with no significant changes in other parameters (113). However, a magnetic resonance imaging study showed that untreated GHD was not associated with impaired systolic function or reduced LV mass, and that 1 year only of GH replacement at physiological doses did not affect cardiac mass or function (114). Similar results were obtained in another investigation, even if a significant decrease in amino-terminal pro-brain natriuretic peptide, a marker of heart failure, was observed after GH replacement (115). Two recent studies did not observe significant improvement in cardiac function or morphology with different dose regimens of GH (low, moderate, or high dose) during a quite short period of treatment (1 y) (116, 117).

Mortality and Cardiovascular Events in Adult GHD

Retrospective studies suggested that hypopituitarism may be associated with significant increased mortality, especially in women (118–123). These studies showed a high prevalence of untreated GHD, whereas other hormone deficiencies were conventionally replaced. This increased mortality seemed to be particularly associated with cardiovascular and cerebrovascular disease (118–123). These findings suggested that a GHD state may expose to and worsen the risk for cardiovascular disease, even if other factors, including GHD etiology (especially craniopharyngioma) and untreated estrogen deficiency could have been additional independent risk factors.

Stochholm et al (124) found significantly increased morbidity in GHD patients. This increased morbidity was due to several risk factors, including unfavorable metabolic profile, leading to cardiovascular diseases in both genders (124). However, at present there are no data on the real incidence of cardiovascular events in large cohorts of GHD patients. Assessment of coronary calcium deposits by computed tomography has been recently validated as a reliable tool to estimate the risk for the development of coronary artery disease (125). Recently, coronary calcium deposits were associated with low IGF-1 levels in patients with untreated GHD, and this was observed also in subjects with low Framingham score and independently of hypertension or insulin resistance (126).

By using the Framingham and European Society of Cardiology scoring systems, Schneider et al (127) observed that GH replacement could reduce the cardiovascular risk by one-half within 2 years with high cholesterol, elevated systolic blood pressure, male sex, and low IGF-1 levels being potential predictors of positive response (127). Interestingly, the cardiovascular risk remained significantly higher in controls than in treated patients after 4 years of follow-up; this suggested a sustained effect of GH therapy. Another study showed that GH replacement could provide protection from fatal myocardial infarctions with rapid time course (121). Data from the KIMS database indicated that mortality rates for GH-replaced patients were similar to those of the background population (128). Furthermore, a meta-analysis of blinded, randomized, placebo-controlled trials showed that GH replacement may have beneficial effects on cardiovascular risk, showing improvement in lean and fat mass, total and LDL cholesterol, and diastolic pressure (20). However, long-term controlled trials on global mortality and the impact of GH treatment on cardiovascular morbidity and mortality are lacking.

Recently, van Bunderen et al (129) demonstrated an increased mortality rate for all-cause mortality in adult GHD treated with GH; in particular, an elevated mortality due to cardiovascular events was observed in women. On the contrary, mortality due to malignancies was not increased in adults receiving GH treatment (129). Gaillard et al (130) analyzed the cause-specific mortality in GHD adults on GH replacement and found that malignancies and cardiovascular and cerebrovascular disease were the most common causes of death. Nevertheless, mortality from cardiovascular diseases was lower in this study than in previous studies (130). It is not clear whether the observed difference in cardiovascular mortality between these studies may be the result of GH replacement only or of improved medical care and adequate control of hypertension and hyperlipidemia. Cerebrovascular mortality remained elevated in GH-treated patients.

Summary of Recent Findings, Open Issues, and Conclusions

Recent findings

The recent meta-analysis by Elbornsson et al (21) confirmed the positive effect of GH treatment on total cholesterol, LDL, and HDL, whereas no positive effects were observed on triglycerides. In addition, it was observed that in patients treated with GH, statin therapy could have a synergistic rather than additive effect on cholesterol levels (27). Long-term treatment with GH was shown to improve the constellation of metabolic parameters of MetS and to have positive effects on body composition (38–40, 43, 44, 48, 49). It has also recently emerged that GH replacement can improve inflammation, as documented by a reduction in CRP (70, 72), TNF-α (76), and IL-6 (70). Positive effects of GH replacement were also observed for several adipokines, such as adiponectin, leptin, and

PAPP-A (81), which may represent not only a marker but also the possible link between GHD, inflammation, and atherosclerosis (10, 92). Conversely, the most recent interventional studies failed to consistently show GH-mediated improvement in cardiac and prognostic outcomes (114–117, 125–127).

Open issues

GHD is associated with an unfavorable pattern of traditional cardiovascular risk factors. Moreover, nontraditional and emerging markers of cardiovascular risk are also altered in adult GHD patients. As a consequence, GHD is characterized by increased cardiovascular mortality and morbidity. GH replacement is expected to improve cardiovascular outcomes of GHD patients. In fact, it was reported by many authors to positively affect both traditional and emerging cardiovascular risk factors. Although initial evidence suggested that these results were linked to a reduced global cardiovascular mortality and morbidity in GHD patients, specific, long-term, and large trials are lacking. However, with our current knowledge about positive effects of GH, albeit on surrogate cardiovascular markers, it might be difficult to get acceptance/approval for (placebo) controlled long-term studies that may be considered unethical. Moreover, interpretation of available studies on hard cardiovascular endpoints is affected by several factors. First, the doses used for GH replacement and the cutoff for interpreting normalization of IGF-1 have been significantly lowered over time (131–134). In fact, from early weight-based dosing derived from pediatric care up to 0.07–0.1 IU/kg daily (135–137), mainly due to side effects (related to fluid retention), adult practice shifted to individualized starting low doses, generally less than 1 IU (200–300 μg) per day (131), gradually titrated until obtaining target IGF-1 in the normal range for age (131, 134). The use of very low doses of GH minimized side effects while producing similar or even better (44) metabolic effects than high doses previously used. In fact, for all metabolic targets, possibly a U-shaped curve may be envisaged with excessively high GH doses leading to an acromegaly-like effect (138–142). Therefore, for patients with longer follow-up, beneficial effects of current low-dose GH regimens may be counterbalanced by potentially harmful effects of initially used high-dose GH. Second, cardiovascular events remain quite a rare occurrence in GHD, which in turn is a rare condition (9), and therefore it is difficult to design studies with these endpoints. On the other hand, this is not a big issue for surrogate markers, the changes of which may well occur, as reported in our review, very early or after relatively short-term trials of GH treatment. In this regard, studies with very long follow-up published in the last few years are reassuring, showing a consistency of the effects of GH on cardiovascular markers/risk factors between positive short-time and long-time responses, and even (as happens for bone effects) (138, 143) a change from negative effects in the short term to positive effects in the long term (glucose metabolism). Third, age of onset of GHD (144) as well as age per se of the patients may be relevant to the definition of a population at high cardiovascular risk, as well as to the expected vs observed events, particularly in terms of length of necessary follow-up (clearly more prolonged for young patients) and in terms of concomitant/coexistent risk factors with high prevalence in the general population (hypertension, diabetes, and obesity) not necessarily linked to GHD. Unfortunately, due to the relative rarity of the disease, mixed populations are involved in the studies in terms of age of onset, sex (females require higher GH doses than males to achieve the same biological effects) (9), etiology (post-Cushing, acromegaly, or craniopharyngioma are subgroups of patients at pre-existing high cardiovascular risk), and additional pituitary defects (eg, cortisol deficiency may often be over-replaced, and this may represent an additional cardiovascular risk factor) (145). Therefore, due to this inhomogeneous composition of the group of GHD adults and awaiting subgroup-specific guidelines, every patient should be evaluated at the individual level. Fourth, the types of studies available on the effects of GH on cardiovascular risk factors/markers but especially on cardiovascular events are also of mixed quality and generally characterized by open, uncontrolled, and observational features. Therefore, selection bias as well as causality of the reported observations can rarely be ruled out. Finally, do we have enough evidence to consider reduction of cardiovascular risk an indication for prescribing GH to GHD patients (146)? This issue is still very sensitive because of the cost of treatment and its potential side effects. Unfortunately, 8 years after our previous review on the topic (9) and despite many further studies having been published, there is still no definitive answer to this question, and therefore cardiovascular effects of GH therapy in GHD should still be considered an expected benefit of treatment but not an indication to it.

Conclusions

Therefore, in conclusion, the GHD population may be considered at high cardiovascular risk, and GH substitution may be expected to bring an added value to patients with hypopituitarism in terms of cardiovascular protection. However, due to limitations of the available data there is too limited evidence (rarely coming from randomized/controlled studies) to recommend GH treatment based on the cardiovascular status of the patients.

Acknowledgments

Address all correspondence and requests for reprints to: Prof Andrea Giustina, Chair of Endocrinology, University of Brescia, A.O. Spedali Civili di Brescia, Scala 7, Piano 2, Piazzale Spedali Civili 1, 25123 Brescia, Italy. E-mail: a.giustina@libero.it.

The study was partially supported by MIUR (Italian Ministry for Education University and Research) and the University of Brescia.

Disclosure Summary: The authors have nothing to disclose.

References

1. **Rosilio M, Blum WF, Edwards DJ, et al.** Long-term improvement of quality of life during growth hormone (GH) replacement therapy in adults with GH deficiency, as measured by questions on life satisfaction-hypopituitarism (QLS-H). *J Clin Endocrinol Metab*. 2004; 89(4):1684–1693.
2. **Koltowska-Häggström M, Mattsson AF, Shalet SM.** Assessment of quality of life in adult patients with GH deficiency: KIMS contribution to clinical practice and pharmacoeconomic evaluations. *Eur J Endocrinol*. 2009;161(suppl 1):S51–S64.
3. **Jørgensen AP, Fougner KJ, Ueland T, et al.** Favorable long-term effects of growth hormone replacement therapy on quality of life, bone metabolism, body composition and lipid levels in patients with adult-onset growth hormone deficiency. *Growth Horm IGF Res*. 2011;21(2):69–75.
4. **Widdowson WM, Gibney J.** The effect of growth hormone replacement on exercise capacity in patients with GH deficiency: a meta-analysis. *J Clin Endocrinol Metab*. 2008;93(11):4413–4417.
5. **Doga M, Bonadonna S, Gola M, Mazziotti G, Nuzzo M, Giustina A.** GH deficiency in the adult and bone. *J Endocrinol Invest*. 2005; 28(8):18–23.
6. **Holmes SJ, Economou G, Whitehouse RW, Adams JE, Shalet SM.** Reduced bone mineral density in patients with adult onset growth hormone deficiency. *J Clin Endocrinol Metab*. 1994;78:669–674.
7. **Canalis E, Giustina A, Bilezikian JP.** Mechanisms of anabolic therapies for osteoporosis. *N Engl J Med*. 2007;357(9):905–916.
8. **Rosén T, Hansson T, Granhed H, Szucs J, Bengtsson BA.** Reduced bone mineral content in adult patients with growth hormone deficiency. *Acta Endocrinol (Copenh)*. 1993;129:201–206.
9. **Gola M, Bonadonna S, Doga M, Giustina A.** Clinical review: growth hormone and cardiovascular risk factors. *J Clin Endocrinol Metab*. 2005;90(3):1864–1870.
10. **Gola M, Giustina A.** Growth hormone deficiency and cardiovascular risk: do we need additional markers? *Endocrine*. 2012;42(2): 240–242.
11. **Abdu TA, Neary R, Elhadd TA, Akber M, Clayton RN.** Coronary risk in growth hormone deficient hypopituitary adults: increased predicted risk is due largely to lipid profile abnormalities. *Clin Endocrinol (Oxf)*. 2001;55(2):209–216.
12. **Gazzaruso C, Coppola A, Montalcini T, et al.** Lipoprotein(a) and homocysteine as genetic risk factors for vascular and neuropathic diabetic foot in type 2 diabetes mellitus. *Endocrine*. 2012;41(1):89–95.
13. **Gazzaruso C, Garzaniti A, Falcone C, Geroldi D, Finardi G, Fratino P.** Association of lipoprotein(a) levels and apolipoprotein(a) phenotypes with coronary artery disease in type 2 diabetic patients and in non-diabetic subjects. *Diabet Med*. 2001;18(7):589–594.
14. **Robinson JG, Wang S, Jacobson TA.** Meta-analysis of comparison of effectiveness of lowering apolipoprotein B versus low-density lipoprotein cholesterol and nonhigh-density lipoprotein cholesterol for cardiovascular risk reduction in randomized trials. *Am J Cardiol*. 2012;110(10):1468–1476.
15. **Svensson J, Fowelin J, Landin K, Bengtsson BA, Johansson JO.** Effects of seven years of GH-replacement therapy on insulin sensitivity in GH-deficient adults. *J Clin Endocrinol Metab*. 2002;87(5):2121–2127.
16. **van der Klaauw AA, Romijn JA, Biermasz NR, et al.** Sustained effects of recombinant GH replacement after 7 years of treatment in adults with GH deficiency. *Eur J Endocrinol*. 2006;155(5):701–708.
17. **Götherström G, Svensson J, Koranyi J, et al.** A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone mass, and metabolic indices. *J Clin Endocrinol Metab*. 2001;86(10):4657–4665.
18. **Colson A, Brooke AM, Walker D, et al.** Growth hormone deficiency and replacement in patients with treated Cushing's disease, prolactinomas and non-functioning pituitary adenomas: effects on body composition, glucose metabolism, lipid status and bone mineral density. *Horm Res*. 2006;66(6):257–267.
19. **Florakis D, Hung V, Kaltsas G, et al.** Sustained reduction in circulating cholesterol in adult hypopituitary patients given low dose titrated growth hormone replacement therapy: a two year study. *Clin Endocrinol (Oxf)*. 2000;53(4):453–459.
20. **Maison P, Griffin S, Nicoue-Beglah M, Haddad N, Balkau B, Chanson P.** Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a Metaanalysis of Blinded, Randomized, Placebo-Controlled Trials. *J Clin Endocrinol Metab*. 2004;89(5):2192–2199.
21. **Elbornsson M, Götherström G, Bosæus I, Bengtsson BÅ, Johannsson G, Svensson J.** Fifteen years of GH replacement improves body composition and cardiovascular risk factors. *Eur J Endocrinol*. 2013;168(5):745–753.
22. **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):3762–3769.
23. **Spielhagen C, Schwahn C, Möller K, et al.** The benefit of long-term growth hormone (GH) replacement therapy in hypopituitary adults with GH deficiency: results of the German KIMS database. *Growth Horm IGF Res*. 2011;21(1):1–10.
24. **Stalenhoef AF, de Graaf J.** Association of fasting and nonfasting serum triglycerides with cardiovascular disease and the role of remnant-like lipoproteins and small dense LDL. *Curr Opin Lipidol*. 2008;19(4):355–361.
25. **Rizzo M, Trepp R, Berneis K, Christ ER.** Atherogenic lipoprotein phenotype and low-density lipoprotein size and subclasses in patients with growth hormone deficiency before and after short-term replacement therapy. *Eur J Endocrinol*. 2007;156(3):361–367.
26. **Salman S, Uzum AK, Telci A, Alagol F, Ozbey NC.** Serum adipokines and low density lipoprotein subfraction profile in hypopituitary patients with growth hormone deficiency. *Pituitary*. 2012; 15(3):386–392.
27. **Monson JP, Jönsson P, Koltowska-Häggström M, Kourides I.** Growth hormone (GH) replacement decreases serum total and LDL-cholesterol in hypopituitary patients on maintenance HMG CoA reductase inhibitor (statin) therapy. *Clin Endocrinol (Oxf)*. 2007; 67(4):623–628.
28. **Hwu CM, Kwok CF, Lai TY, et al.** Growth hormone (GH) replacement reduces total body fat and normalizes insulin sensitivity in GH-deficient adults: a report of one-year clinical experience. *J Clin Endocrinol Metab*. 1997;82(10):3285–3292.
29. **Yuen KC, Dunger DB.** Impact of treatment with recombinant human GH and IGF-I on visceral adipose tissue and glucose homeostasis in adults. *Growth Horm IGF Res*. 2006;16(suppl A):S55–S61.
30. **Bülow B, Link K, Ahrén B, Nilsson AS, Erfurth EM.** Survivors of childhood acute lymphoblastic leukaemia, with radiation-induced GH deficiency, exhibit hyperleptinaemia and impaired insulin sensitivity, unaffected by 12 months of GH treatment. *Clin Endocrinol (Oxf)*. 2004;61(6):683–691.
31. **Hana V, Silha JV, Justova V, Lacinova Z, Stepan JJ, Murphy LJ.** The effects of GH replacement in adult GH-deficient patients: changes in

body composition without concomitant changes in the adipokines and insulin resistance. *Clin Endocrinol (Oxf)*. 2004;60(4):442–450.
32. **Bramnert M, Segerlantz M, Laurila E, Daugaard JR, Manhem P, Groop L.** Growth hormone replacement therapy induces insulin resistance by activating the glucose-fatty acid cycle. *J Clin Endocrinol Metab*. 2003;88(4):1455–1463.
33. **Gillberg P, Bramnert M, Thorén M, Werner S, Johannsson G.** Commencing growth hormone replacement in adults with a fixed low dose. Effects on serum lipoproteins, glucose metabolism, body composition, and cardiovascular function. *Growth Horm IGF Res*. 2001;11(5):273–281.
34. **Arwert LI, Roos JC, Lips P, Twisk JW, Manoliu RA, Drent ML.** Effects of 10 years of growth hormone (GH) replacement therapy in adult GH-deficient men. *Clin Endocrinol (Oxf)*. 2005;63(3):310–316.
35. **Spina LD, Soares DV, Brasil RR, Lobo PM, Lúcia Conceição F, Vaisman M.** Glucose metabolism and visceral fat in GH deficient adults: two years of GH-replacement. *Pituitary*. 2004;7(3):123–129.
36. **Boguszewski CL, Meister LH, Zaninelli DC, Radominski RB.** One year of GH replacement therapy with a fixed low-dose regimen improves body composition, bone mineral density and lipid profile of GH-deficient adults. *Eur J Endocrinol*. 2005;152(1):67–75.
37. **Spina LD, Soares DV, Brasil RR, et al.** Glucose metabolism and visceral fat in GH deficient adults: 1 year of GH replacement. *Growth Horm IGF Res*. 2004;14(1):45–51.
38. **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. *Metabolism*. 2008;57(1):121–129.
39. **Roemmler J, Kuenkler M, Schneider HJ, Dieterle C, Schopohl J.** Comparison of glucose and lipid metabolism and bone mineralization in patients with growth hormone deficiency with and without long-term growth hormone replacement. *Metabolism*. 2010;59(3):350–358.
40. **Oliveira CR, Salvatori R, Barreto-Filho JA, et al.** Insulin sensitivity and β-cell function in adults with lifetime, untreated isolated growth hormone deficiency. *J Clin Endocrinol Metab*. 2012;97(3):1013–1019.
41. **Giavoli C, Porretti S, Ronchi CL, et al.** Long-term monitoring of insulin sensitivity in growth hormone-deficient adults on substitutive recombinant human growth hormone therapy. *Metabolism*. 2004;53(6):740–743.
42. **Sesmilo G, Biller BM, Llevadot J, et al.** Effects of growth hormone administration on inflammatory and other cardiovascular risk markers in men with growth hormone deficiency. A randomized, controlled clinical trial. *Ann Intern Med*. 2000;133(2):111–122.
43. **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):2063–2071.
44. **Arafat AM, Möhlig M, Weickert MO, Schöfl C, Spranger J, Pfeiffer AF.** 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):1304–1313.
45. **Nikolopoulou A, Kadoglou NP.** Obesity and metabolic syndrome as related to cardiovascular disease. *Expert Rev Cardiovasc Ther*. 2012;10(7):933–939.
46. **Ma X, Zhu S.** Metabolic syndrome in the prevention of cardiovascular diseases and diabetes–still a matter of debate? *Eur J Clin Nutr*. 2013;67(5):518–521.
47. **Gazzaruso C, Solerte SB, De Amici E, et al.** Association of the metabolic syndrome and insulin resistance with silent myocardial ischemia in patients with type 2 diabetes mellitus. *Am J Cardiol*. 2006;97(2):236–239.
48. **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):455–462.
49. **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.
50. **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):2255–2262.
51. **Filipsson H, Monson JP, Koltowska-Häggström M, Mattsson A, Johannsson G.** The impact of glucocorticoid replacement regimens on metabolic outcome and comorbidity in hypopituitary patients. *J Clin Endocrinol Metab*. 2006;91(10):3954–3961.
52. **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(1):79–90.
53. **Götherström G, Bengtsson BA, Bosaeus I, Johannsson G, Svensson J.** A 10-year, prospective study of the metabolic effects of growth hormone replacement in adults. *J Clin Endocrinol Metab*. 2007;92(4):1442–1445.
54. **Colao A, Di Somma C, Spiezia S, et al.** Growth hormone treatment on atherosclerosis: results of a 5-year open, prospective, controlled study in male patients with severe growth hormone deficiency. *J Clin Endocrinol Metab*. 2008;93(9):3416–3424.
55. **Kahn R, Buse J, Ferrannini E, Stern M.** The metabolic syndrome: time for a critical appraisal. Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia*. 2005;48(9):1684–1699.
56. **Simmons RK, Alberti KG, Gale EA, et al.** The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation. *Diabetologia*. 2010;53(4):600–605.
57. **Vahl N, Juul A, Jørgensen JO, Orskov H, Skakkebaek NE, Christiansen JS.** Continuation of growth hormone (GH) replacement in GH-deficient patients during transition from childhood to adulthood: a two-year placebo-controlled study. *J Clin Endocrinol Metab*. 2000;85(5):1874–1881.
58. **Johannsson G, Albertsson-Wikland K, Bengtsson BA.** Discontinuation of growth hormone (GH) treatment: metabolic effects in GH-deficient and GH-sufficient adolescent patients compared with control subjects. Swedish Study Group for Growth Hormone Treatment in Children. *J Clin Endocrinol Metab*. 1999;84(12):4516–4524.
59. **Attanasio AF, Shavrikova E, Blum WF, et al.** Continued growth hormone (GH) treatment after final height is necessary to complete somatic development in childhood-onset GH-deficient patients. *J Clin Endocrinol Metab*. 2004;89(10):4857–4862.
60. **Tauber M, Jouret B, Cartault A, et al.** Adolescents with partial growth hormone (GH) deficiency develop alterations of body composition after GH discontinuation and require follow-up. *J Clin Endocrinol Metab*. 2003;88(11):5101–5106.
61. **Mauras N, Pescovitz OH, Allada V, Messig M, Wajnrajch MP, Lippe B.** Limited efficacy of growth hormone (GH) during transition of GH-deficient patients from adolescence to adulthood: a phase III multicenter, double-blind, randomized two-year trial. *J Clin Endocrinol Metab*. 2005;90(7):3946–3955.
62. **Rietzschel E, De Buyzere M.** High-sensitive C-reactive protein: universal prognostic and causative biomarker in heart disease? *Biomark Med*. 2012;6(1):19–34.
63. **Bisoendial RJ, Boekholdt SM, Vergeer M, Stroes ES, Kastelein JJ.** C-reactive protein is a mediator of cardiovascular disease. *Eur Heart J*. 2010;31(17):2087–2091.
64. **Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM.** C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*. 2001;286(3):327–334.
65. **Hu G, Jousilahti P, Tuomilehto J, Antikainen R, Sundvall J, Salomaa V.** Association of serum C-reactive protein level with sex-specific

type 2 diabetes risk: a prospective Finnish study. *J Clin Endocrinol Metab*. 2009;94(6):2099–2105.
66. **Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM.** C-reactive protein and the risk of developing hypertension. *JAMA*. 2003;290(22):2945–2951.
67. **Yang T, Chu CH, Hsieh PC, et al.** C-reactive protein concentration as a significant correlate for metabolic syndrome: a Chinese population-based study. *Endocrine*. 2013;43(2):351–359.
68. **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 Chim Acta*. 2006;370(1–2):50–56.
69. **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 (Oxf)*. 2005;62(4):473–479.
70. **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):537–543.
71. **Sesmilo G, Miller KK, Hayden D, Klibanski A.** Inflammatory cardiovascular risk markers in women with hypopituitarism. *J Clin Endocrinol Metab*. 2001;86(12):5774–5781.
72. **Deepak D, Daousi C, Javadpour M, et al.** The influence of growth hormone replacement on peripheral inflammatory and cardiovascular risk markers in adults with severe growth hormone deficiency. *Growth Horm IGF Res*. 2010;20(3):220–225.
73. **Libby P.** Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2012;32(9):2045–2051.
74. **Wong BW, Meredith A, Lin D, McManus BM.** The biological role of inflammation in atherosclerosis. *Can J Cardiol*. 2012;28(6):631–641.
75. **Serri O, St-Jacques P, Sartippour M, Renier G.** Alterations of monocyte function in patients with growth hormone (GH) deficiency: effect of substitutive GH therapy. *J Clin Endocrinol Metab*. 1999;84(1):58–63.
76. **Andiran N, Yordam N.** TNF-alpha levels in children with growth hormone deficiency and the effect of long-term growth hormone replacement therapy. *Growth Horm IGF Res*. 2007;17(2):149–153.
77. **Pardo M, Roca-Rivada A, Seoane LM, Casanueva FF.** Obesidomics: contribution of adipose tissue secretome analysis to obesity research. *Endocrine*. 2012;41(3):374–383.
78. **Sahin-Efe A, Katsikeris F, Mantzoros CS.** Advances in adipokines. *Metabolism*. 2012;61(12):1659–1665.
79. **Brochu-Gaudreau K, Rehfeldt C, Blouin R, Bordignon V, Murphy BD, Palin MF.** Adiponectin action from head to toe. *Endocrine*. 2010;37(1):11–32.
80. **Kim HS, Jo J, Lim JE, et al.** Adiponectin as predictor for diabetes among pre-diabetic groups. [published online ahead of print February 06, 2013] *Endocrine*. doi:10.1007/s12020–013–9890–5.
81. **Chaves VE, Júnior FM, Bertolini GL.** The metabolic effects of growth hormone in adipose tissue. *Endocrine*. 2013;44(2):293–302.
82. **Miyakawa M, Tsushima T, Murakami H, Isozaki O, Demura H, Tanaka T.** 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):3476–3479.
83. **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 (Oxf)*. 2004;61(1):81–87.
84. **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):812–817.
85. **Florkowski CM, Collier GR, Zimmet PZ, Livesey JH, Espiner EA, Donald RA.** Low-dose growth hormone replacement lowers plasma leptin and fat stores without affecting body mass index in adults with growth hormone deficiency. *Clin Endocrinol (Oxf)*. 1996;45(6):769–773.
86. **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):663–665.
87. **López-Siguero JP, López-Canti LF, Espino R, et al.** Effect of recombinant growth hormone on leptin, adiponectin, resistin, interleukin-6, tumor necrosis factor-α and ghrelin levels in growth hormone-deficient children. *J Endocrinol Invest*. 2011;34(4):300–306.
88. **Conti E, Carrozza C, Capoluongo E, et al.** Insulin-like growth factor-1 as a vascular protective factor. *Circulation*. 2004;110(15):2260–2265.
89. **Heeschen C, Dimmeler S, Hamm CW, Fichtlscherer S, Simoons ML, Zeiher AM.** Pregnancy-associated plasma protein-A levels in patients with acute coronary syndromes: comparison with markers of systemic inflammation, platelet activation, and myocardial necrosis. *J Am Coll Cardiol*. 2005;45(2):229–237.
90. **Fialová L, Pilecková N, Bauer J, et al.** Pregnancy-associated plasma protein-A in patients with cerebrovascular diseases–a pilot study. *Prague Med Rep*. 2006;107(1):37–45.
91. **Joaquin C, Aguilera E, et al.** Effects of GH treatment in GH-deficient adults on adiponectin, leptin and pregnancy-associated plasma protein-A. *Eur J Endocrinol*. 2008;158(4):483–490.
92. **Li L, Ren W, Li J, et al.** 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):375–381.
93. **Smith JC, Lang D, McEneny J, et al.** Effects of GH on lipid peroxidation and neutrophil superoxide anion-generating capacity in hypopituitary adults with GH deficiency. *Clin Endocrinol (Oxf)*. 2002;56(4):449–455.
94. **González-Duarte D, Madrazo-Atutxa A, Soto-Moreno A, Leal-Cerro A.** Measurement of oxidative stress and endothelial dysfunction in patients with hypopituitarism and severe deficiency adult growth hormone deficiency. *Pituitary*. 2012;15(4):589–597.
95. **Ozbey N, Telci A, Cakatay U, Yurci A, Molvalilar S.** Determination of oxidative protein and lipid damage in adult hypopituitary patients with GH deficiency. *J Endocrinol Invest*. 2003;26(10):1001–1007.
96. **Scacchi M, Valassi E, Pincelli AI, et al.** Increased lipid peroxidation in adult GH-deficient patients: effects of short-term GH administration. *J Endocrinol Invest*. 2006;29(10):899–904.
97. **Sanz J, Moreno PR, Fuster V.** The year in atherothrombosis. *J Am Coll Cardiol*. 2012;60(10):932–942.
98. **Jax TW, Peters AJ, Plehn G, Schoebel FC.** Hemostatic risk factors in patients with coronary artery disease and type 2 diabetes - a two year follow-up of 243 patients. *Cardiovasc Diabetol*. 2009;8:48.
99. **Cakir I, Tanriverdi F, Karaca Z, et al.** Evaluation of coagulation and fibrinolytic parameters in adult onset GH deficiency and the effects of GH replacement therapy: a placebo controlled study. *Growth Horm IGF Res*. 2012;22(1):17–21.
100. **Beshyah SA, Markussis V, Harbourne T, Nicolaides AN, Johnston DG.** Haemostatic mechanisms are normal despite increased vascular mortality in hypopituitary adults. *Horm Metab Res*. 1993;25(8):449–450.
101. **Gómez JM, Sahún M, Vila R, et al.** Peripheral fibrinolytic markers, soluble adhesion molecules, inflammatory cytokines and endothelial function in hypopituitary adults with growth hormone deficiency. *Clin Endocrinol (Oxf.)* 2006;64(6):632–639.
102. **Kvasnicka J, Marek J, Kvasnicka T, et al.** Increase of adhesion molecules, fibrinogen, type-1 plasminogen activator inhibitor and orosomucoid in growth hormone (GH) deficient adults and their modulation by recombinant human GH replacement. *Clin Endocrinol (Oxf)*. 2000;52(5):543–548.
103. **Johansson JO, Landin K, Johannsson G, Tengborn L, Bengtsson BA.** Long-term treatment with growth hormone decreases plasminogen activator inhibitor-1 and tissue plasminogen activator in growth hormone-deficient adults. *Thromb Haemost*. 1996;76(3):422–428.

104. **Gazzaruso C, Coppola A, Giustina A.** Erectile dysfunction and coronary artery disease in patients with diabetes. *Curr Diabetes Rev*. 2011;7(2):143–147.
105. **Siervo M, Corander M, Stranges S, Bluck L.** Post-challenge hyperglycaemia, nitric oxide production and endothelial dysfunction: the putative role of asymmetric dimethylarginine (ADMA). *Nutr Metab Cardiovasc Dis*. 2011;21(1):1–10.
106. **Krzyzanowska K, Mittermayer F, Schnack C, Hofer M, Wolzt M, Schernthaner G.** Circulating ADMA concentrations are elevated in hypopituitary adults with and without growth hormone deficiency. *Eur J Clin Invest*. 2005;35(3):208–213.
107. **Setola E, Monti LD, Lanzi R, et al.** Effects of growth hormone treatment on arginine to asymmetric dimethylarginine ratio and endothelial function in patients with growth hormone deficiency. *Metabolism*. 2008;57(12):1685–1690.
108. **Juárez-Orozco LE, Glauche J, Alexanderson E, et al.** Myocardial perfusion reserve in spared myocardium: correlation with infarct size and left ventricular ejection fraction. *Eur J Nucl Med Mol Imaging*. 2013;40(8):1148–1154.
109. **Giubbini R, Bertagna F.** Myocardial perfusion reserve in spared myocardium: one more tessera of the complex mosaic of LV remodelling after myocardial infarction. *Eur J Nucl Med Mol Imaging*. 2013;40(8):1146–1147.
110. **Moisey R, Orme S, Barker D, et al.** Cardiac functional reserve is diminished in growth hormone-deficient adults. *Cardiovasc Ther*. 2009;27(1):34–41.
111. **Groban L, Lin M, Kassik KA, Ingram RL, Sonntag WE.** Early-onset growth hormone deficiency results in diastolic dysfunction in adult-life and is prevented by growth hormone supplementation. *Growth Horm IGF Res*. 2011;21:81–88.
112. **Maison P, Chanson P.** Cardiac effects of growth hormone in adults with growth hormone deficiency: a meta-analysis. *Circulation*. 2003;108:2648–2652.
113. **Cenci MC, Soares DV, Spina LD, et al.** Effects of 5 years of growth hormone (GH) replacement therapy on cardiac parameters and physical performance in adults with GH deficiency. *Pituitary*. 2009;12:322–329.
114. **Andreassen M, Faber J, Kjaer A, Petersen CL, Kristensen LØ.** Cardiac function in growth hormone deficient patients before and after 1 year with replacement therapy: a magnetic resonance imaging study. *Pituitary*. 2011;14:1–10.
115. **Gruson D, Alexopoulou O, Pasquet A, Cumps J, Ketelslegers JM, Maiter D.** 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; 72:387–394.
116. **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 Horm IGF Res*. 2012;22:116–121.
117. **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;96:122–132.
118. **Rosén T, Bengtsson BA.** Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet*. 1990;336(8710):285–288.
119. **Bates AS, Van't Hoff W, Jones PJ, Clayton RN.** The effect of hypopituitarism on life expectancy. *J Clin Endocrinol Metab*. 1996; 81(3):1169–1172.
120. **Bülow B, Hagmar L, Mikoczy Z, Nordström CH, Erfurth EM.** Increased cerebrovascular mortality in patients with hypopituitarism. *Clin Endocrinol (Oxf)*. 1997;46(1):75–81.
121. **Svensson J, Bengtsson BA, Rosén T, Odén A, Johannsson G.** Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. *J Clin Endocrinol Metab*. 2004;89(7):3306–3312.
122. **Tomlinson JW, Holden N, Hills RK, et al.** Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. *Lancet*. 2001;357(9254): 425–431.
123. **Burman P, Mattsson AF, Johannsson G, et al.** Deaths among adult patients with hypopituitarism: hypocortisolism during acute stress, and de novo malignant brain tumors contribute to an increased mortality. *J Clin Endocrinol Metab*. 2013;98(4):1466–1475.
124. **Stochholm K, Laursen T, Green A, et al.** Morbidity and GH deficiency: a nationwide study. *Eur J Endocrinol*. 2008;158(4):447–457.
125. **Vliegenthart R, Morris PB.** Computed tomography coronary artery calcium scoring: review of evidence base and cost-effectiveness in cardiovascular risk prediction. *J Thorac Imaging*. 2012;27(5): 296–303.
126. **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): 32–37.
127. **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 (Oxf)*. 2011;75(6): 825–830.
128. **Monson JP.** Long-term experience with GH replacement therapy: efficacy and safety. *Eur J Endocrinol*. 2003;148(suppl 2): S9–S14.
129. **van Bunderen CC, van Nieuwpoort IC, Arwert LI, et al.** Does growth hormone replacement therapy reduce mortality in adults with growth hormone deficiency? Data from the Dutch National Registry of Growth Hormone Treatment in adults. *J Clin Endocrinol Metab*. 2011;96(10):3151–3159.
130. **Gaillard RC, Mattsson AF, Akerblad AC, et al.** Overall and cause-specific mortality in GH-deficient adults on GH replacement. *Eur J Endocrinol*. 2012;166(6):1069–1077.
131. **Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML.** Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(6):1587–1609.
132. **Doga M, Bonadonna S, Gola M, Mazziotti G, Giustina A.** Growth hormone deficiency in the adult. *Pituitary*. 2006;9(4):305–311.
133. **Doga M, Bonadonna S, Gola M, et al.** Current guidelines for adult GH replacement. *Rev Endocr Metab Disord*. 2005;6(1):63–70.
134. **Giustina A, Barkan A, Chanson P, et al.** Guidelines for the treatment of growth hormone excess and growth hormone deficiency in adults. *J Endocrinol Invest*. 2008;31(9):820–38.
135. **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 (Lond)*. 1991;81(5):587–592.
136. **Johannsson G, Bengtsson BA, Andersson B, Isgaard J, Caidahl K.** Long-term cardiovascular effects of growth hormone treatment in GH-deficient adults. Preliminary data in a small group of patients. *Clin Endocrinol (Oxf)*. 1996;45(3):305–314.
137. **Johannsson G, Rosén T, Bengtsson BA.** Individualized dose titration of growth hormone (GH) during GH replacement in hypopituitary adults. *Clin Endocrinol (Oxf)*. 1997;47(5):571–581.
138. **Giustina A, Mazziotti G, Canalis E.** Growth hormone, insulin-like growth factors, and the skeleton. *Endocr Rev*. 2008;29(5):535–559.
139. **Mazziotti G, Gola M, Bianchi A, et al.** Influence of diabetes mellitus on vertebral fractures in men with acromegaly. *Endocrine*. 2011;40(1):102–108.
140. **Melmed S, Casanueva FF, Klibanski A, et al.** A consensus on the diagnosis and treatment of acromegaly complications. *Pituitary*. 2013;16(3):294–302.

141. **Maison P, Tropeano AI, Macquin-Mavier I, Giustina A, Chanson P.** Impact of somatostatin analogs on the heart in acromegaly: a metaanalysis. *J Clin Endocrinol Metab*. 2007;92(5):1743–1747.
142. **Giustina A, Casanueva FF, Cavagnini F, et al.** Diagnosis and treatment of acromegaly complications. *J Endocrinol Invest*. 2003;26(12):1242–1247.
143. **Mazziotti G, Bianchi A, Bonadonna S, et al.** Increased prevalence of radiological spinal deformities in adult patients with GH deficiency: influence of GH replacement therapy. *J Bone Miner Res*. 2006;21(4):520–528.
144. **Attanasio AF, Lamberts SW, Matranga AM, et al.** Adult growth hormone (GH)-deficient patients demonstrate heterogeneity between childhood onset and adult onset before and during human GH treatment. Adult Growth Hormone Deficiency Study Group. *J Clin Endocrinol Metab*. 1997;82(1):82–88.
145. **Mazziotti G, Porcelli T, Bianchi A, et al.** Glucocorticoid replacement therapy and vertebral fractures in hypopituitary adult males with GH deficiency. *Eur J Endocrinol*. 2010;163(1):15–20.
146. **Giustina A.** Does growth hormone replacement therapy improve cardiac function? *Nat Clin Pract Endocrinol Metab*. 2007;3(9):614–615.