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Review

Impact of adult growth hormone deficiency on metabolic profile and cardiovascular risk

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Abstract. Adult growth hormone deficiency (GHD) is a well defined clinical condition, which is characterized by abnormal body composition, impaired physical activity and decreased quality of life. In addition, in recent years, growing interest has been shown towards cardiovascular risks in adult patients affected by GHD. In this regard, GHD is widely known to be associated with increased mortality, likely due to the increase of risk factors, such as central obesity, impaired lipid and glucose profiles and other less-known risk factors, such as inflammatory cytokines, endothelial dysfunction and oxidative stress. However, very few papers have recently discussed this topic. In this review, the aim is to clarify this issue by discussing evidence regarding the effects of adult GHD on metabolic and cardiovascular profiles.

Key words: Growth hormone, Deficiency, Cardiovascular risk factor, Pituitary, Hormonal treatment

GROWTH HORMONE DEFICIENCY (GHD) in adults is a well-defined clinical condition, characterized by abnormal body composition, impaired physical activities as well as decreased quality of life; in addition, in recent years, growing interest has been shown towards cardiovascular risk in adult patients affected by GHD [1-9]. In light of the scantiness of recent specific reviews on this subject, in this paper we review the evidence of the metabolic and cardiovascular effects of GHD on adult patients.

Diagnosis of GHD: a brief overview

Three groups of adults affected by GHD have been included in the studies:

1) Patients with a previous diagnosis of childhood GHD (CO-GHD);
2) Patients with GHD caused by trauma or structural lesions at hypothalamic-pituitary level;
3) Patients affected by idiopathic GHD (very rare).

2011 Endocrine society guidelines recommend to evaluate as potentially affected by acquired GHD every adult who is either affected by hypothalamic-pituitary diseases or who has undergone surgery or irradiation in these regions or who has suffered from head trauma or even with biochemical evidence of pituitary hormone deficiency [10]. Diagnosis is made on the basis of stimulus tests, such as insulin tolerance test (ITT) and GH releasing hormone (GHRH) + arginine test (Table 1). However, it must be remembered that biochemical criteria for the diagnosis of adult GHD does not envisage age-, sex-, and body mass index (BMI)-specific cutoffs; in addition, a certain degree of variability exists both in assay methods and in stimulus test protocols. According to a multicenter study, which used a sensitive, immunochemiluminescent two-site assay, the GH values of 5.1 μ/L for the ITT and 4.1 μ/L for GHRH-arginine test had sufficient specificity and sensitivity for the diagnosis of adult GHD [11]. Moreover, many European studies have proposed to adjust the cutoffs for GHRH + arginine test depending on BMI values.

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Table 1 Diagnosis of adult GHD

Adult GHD	Diagnostic tests
• Patients with CO-GHD due to genetic mutation, embriogenetic lesions or irreversible damage of hypothalamus-pituitary system causing at least 3 or more hormonal deficits	• Not required
• Patients with acquired GHD (head injury, hypothalamus-pituitary system disorders, irradiation or surgery of these regions) having less than 3 pituitary hormonal deficits	• GHRH + Arginine test or insulin tolerance test Glucagon test
• Patients with idiopathic GHD	
• Patients with idiopathic and isolated CO-GHD	• Gold standard: GHRH + Arginine test

GHD, growth hormone deficiency; GHRH, growth hormone releasing hormone; CO-GHD, childhood GHD

In particular, Corneli *et al.* showed that the appropriate cut-points for diagnosing GHD were 11.5 μ/L for those with a BMI less than 25 kg/m^2, 8.0 μ/L for a BMI of 25–30 kg/m^2, and 4.2 μ/L for those with a BMI greater than 30 kg/m^2 [12]. However, when GHRH is not available and ITT is either contraindicated or not practicable, the glucagon stimulation test can be useful for diagnosing GHD. When the glucagon test is used, a cut-point of between 2.5 and 3 μ/L has been shown to have adequate specificity and sensitivity for the diagnosis of GHD [10] (Table 1).

1. Metabolic effects

1.a Glucose metabolism and insulin resistance

GHD is often associated with impaired glucose metabolism, characterised by insulin resistance and fasting hyperinsulinemia [6, 13]. Recently, the KIMS (Pfizer International Metabolic Database) study, which was carried out in 6050 GHD patients who were not undergoing the relevant replacement therapy, showed an increased prevalence of type 2 diabetes mellitus, especially in women, mainly due to increased BMI and to the impaired body composition; furthermore, 9.5% of nondiabetic patients presented glycated haemoglobin (HbA1c) values between 6 and 6.5% [14]. The increased prevalence of type 2 diabetes in patients with GH deficiency is likely due to the increased insulin resistance, particularly at hepatic level, and to the inadequate beta cell ability to counteract insulin resistance [15, 16]. However, the effects of GH replacement therapy on glucose metabolism are controversial. Bramnert *et al.* evaluated the effects of GH replacement therapy in 19 GHD patients after 1 week and after 6 months of treatment [17]. Hormone therapy induced an impaired insulin-induced glucose uptake after one week (-52%; $P = 0.008$) and after six months (-39%; $P = 0.008$), which correlated with deterioration of glucose tolerance ($r = -0.481$; $P = 0.003$). Therefore, that report highlighted that both reduced glucose uptake and impaired glucose metabolism are associated with increased lipid oxidation due to lipolitic GH action. A worsening of glucose metabolism has also been observed in other studies with a follow-up of 12 months [18, 19]. However, in this regard, it is worth mentioning that duration of therapy may represent a confounding factor. A study evaluating 14 GHD patients, who were treated with hormone replacement therapy and evaluated every 3 months for 5 years, showed that glycemia and fasting insulin as well as homeostasis model assessment-estimated insulin resistance (HOMA-IR) index did not change significantly, whereas, after two years of GH replacement therapy, an improvement of glycaemia levels after oral glucose tolerance test was observed [20]. An improvement of oral glucose tolerance test was confirmed also by a work conducted on 22 subjects who were undergoing GH replacement therapy for about ten years [21]. A recent monocentric, prospective and open-label report by Elborsson *et al.* evaluated 156 hypopituitary GHD subjects undergoing GH replacement therapy for about fifteen years [22]. Fasting glycemia rose from 4.4 to 4.8 mmol/L during the study period ($P<0.001$), whereas HbA1c improved from 5.0 to 4.6 % ($P<0.001$). In conclusion, results on this subject are controversial. However, GH replacement therapy seems to exert a biphasic action. In the initial phase, a deterioration of glucose metabolism probably occurs due to decreased peripheral uptake of glucose, whereas, in the long term, low dosage of GH therapy leads to improved glycemia and insulin levels, likely due to a variation of body composition (Fig. 1) [23].

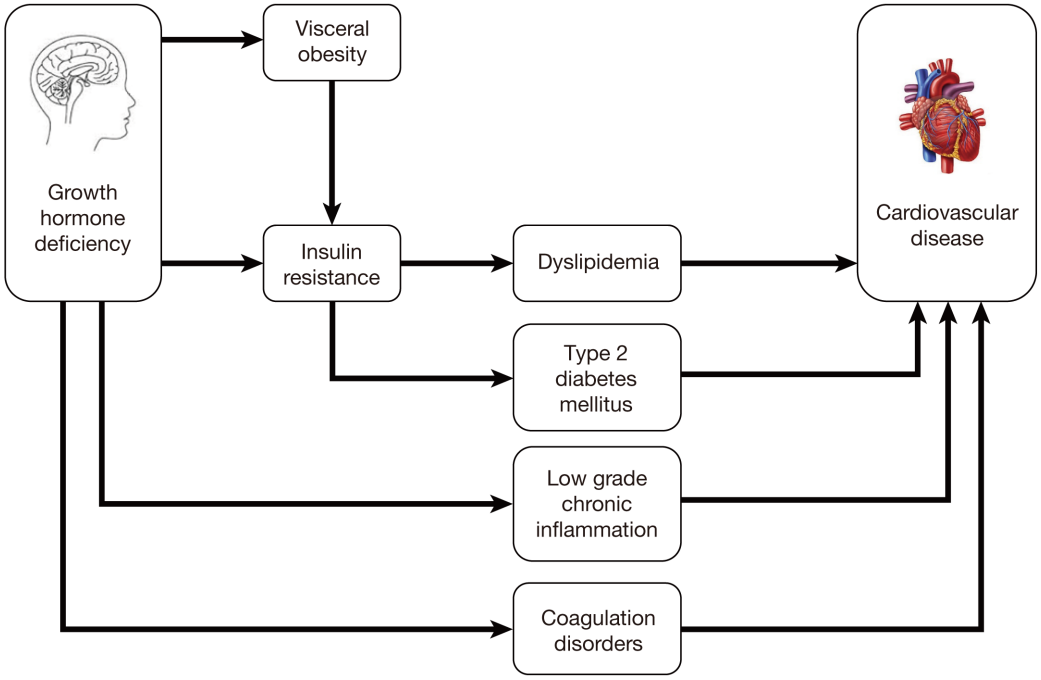

Fig. 1 Growth hormone deficiency and cardiovascular risk. Growth hormone deficiency has been associated with an increase of cardiovascular risk, due to an impairment of body composition, especially in visceral adipose tissue, and subsequent insulin resistance. Growth hormone deficiency has also been associated with glucose metabolism impairment, dyslipidemia, coagulation disorders and chronic inflammation, which globally concur to the increase of cardiovascular risk.

1.b Lipid metabolism

It is well-proven that the increase of low density lipoprotein (LDL) cholesterol and abdominal fat together with the decrease of high density lipoprotein (HDL) cholesterol can augment cardiovascular mortality and morbidity [24]. Lipid serum concentration strictly depends on production and clearance of apolipoprotein (apo) B contained in very low density lipoprotein (VLDL) and lipid metabolism is linked to the one of VLDL apo B, as they are precursors of intermediate density lipoprotein (IDL) and LDL apo B. Several lipid metabolism disorders, which lead to the early onset of atherosclerosis, are caused by hepatic hyperproduction of VLDL apo B [25].

GHD patients usually show increased levels of total and LDL cholesterol [26, 27], whereas more controversial results have been found regarding triglycerides and HDL [7, 28]. A study by Abdu *et al.* evaluated lipid profile and cardiovascular risk by the Framingham score equation in GHD patients and age- and sex-matched controls [29]. That study showed, in both sexes, the increase of total/HDL cholesterol ratio, LDL cholesterol and the reduction of HDL cholesterol (especially in women), thus theoretically explaining the increase of cardiovascular risk in GHD patients.

It has been recently demonstrated that small dense LDL (sdLDL) is an independent cardiovascular risk factor and a report by Rizzo *et al.* found a greater presence of sdLDL in GHD patients [30].

As far as triglyceride metabolism is concerned, an important paper has evaluated the effects of acute GHD induced by pegvisomant [31]. In those subjects, it was observed that pegvisomant treatment alone increased serum triglycerides, thus suggesting a key-role of GH in triglyceride metabolism regulation. Other studies have demonstrated the association between GH and triglycerides; of note, a reduction of triglycerides after recombinant IGF-1 therapy has been observed [32], as well as an opposite correlation between insulin-like growth factor-1 (IGF-1) and triglycerides levels in elderly subjects [33]. Long-term GH replacement therapy (5-10 years) can lead to an improvement of lipid profile. Gotherstrom *et al.*, in a prospective and monocentric study, demonstrated the decrease of total cholesterol and increase of HDL after a 5-year therapy in 118 GHD patients [34]. Similar results have also been obtained in other prospective and monocentric studies [35, 36], where after 7 years of GH replacement ther-

apy an improvement of total and LDL cholesterol was evident, although no effect was observed on triglyceride levels. This finding was confirmed also in a recent prospective and long term study (15 years) conducted on 156 hypopituitary patients [22]. The neutral effect on triglyceride levels has also been observed in a meta-analysis which considered 37 blinded, randomized placebo-control trials involving adult patients undergoing GH replacement therapy; at the same time the positive effect on total and LDL cholesterol was confirmed [37] (Fig. 1).

1.c Body composition

Although the main peripheral targets of GH are represented by bone and muscle, GH is also able to promote lipolysis. Patients with isolated GHD have more abundant fat stores than healthy subjects because of the greater volume of adipose cells [38, 39]. Therefore, the impaired body composition results in a prevalent central fat distribution due to visceral fat accumulation with consequent increase of cardiovascular risk. In fact, low IGF-1 levels determine the increase of fat mass and the decrease of lean mass. Many studies have aimed to clarify this aspect. Various investigators demonstrated that fat mass was higher by around 7% in GHD patients compared with age, sex and height adjusted predicted values [40]. Similarly, Attanasio *et al.* found that metabolic syndrome prevalence was increased in GHD patients [41].

An observational monocentric study by Ukropec *et al.* which evaluated 16 GHD patients and 16 healthy subjects, reported that GHD patients with BMI of approximately 23 kg/m^2 had higher values of waist circumference and visceral fat compared to controls [42]. Another recent monocentric work conducted on 23 adult patients with congenital GHD who were evaluated by (dual-energy x-ray absorptiometry) DEXA, showed that these patients had a greater amount of abdominal and visceral fat than healthy subjects [43].

As far as the effects of GH replacement therapy are concerned, two different double blind, randomized, placebo controlled trials carried out in GH-treated men and women reported a significant decrease of total body and trunk fat and an increase of lean body mass over baseline [37, 44]. The reduction of waist/hip ratio has also been demonstrated by several prospective monocentric studies, which found an improvement of body composition especially in elderly GHD patients (>65 years) compared to the younger ones [45-47]. Furthermore, a recent work assessing GHD patients under 15 years-replacement therapy reported a 3% increase of lean mass compared to baseline [22] (Fig. 1).

2. Inflammatory markers and cardiovascular risk

C-reactive protein (CRP) is a well-known cardiovascular risk factor [48]. Both normoweight and obese GHD patients have a 4-5 fold increase of CRP levels, testifying the presence of a proinflammatory state [49]. Sesmilo *et al.* found an inverse correlation between CRP and IGF-1 levels in hypopituitary women affected by GHD [50] and Deepak *et al.* demonstrated an improvement of inflammation indexes, especially high sensitivity CRP, after 6 months of GH replacement therapy in 15 adult GHD patients (11 males) [51]. Similarly, pro-inflammatory cytokines, especially interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α), play a role in the increase of cardiovascular risk of GHD mainly in consequence of their effect on endothelium [52, 53]. Of note, adipokines, peptides secreted by adipose tissue which also have endocrine, paracrine and autocrine actions are worthy of consideration [52, 53]. Circulating adipokines are represented by adiponectin, which has anti-inflammatory, antiatherogenic and insulin-sensitizing effect and by leptin which has instead prothrombotic, atherogenetic, prooxidative and angiogenetic actions as well as hypertrophic effect on smooth muscle [54].

In GHD patients, an increase of IL-6 levels has been reported, independently of BMI, and of TNF-α values, which decreased after GH replacement therapy [55, 56]. Some Authors have demonstrated an increase of leptin values in GHD patients [57, 58]. The relationship between increased levels of leptin and GHD has been observed in clinical trials involving subjects undergoing hormonal replacement therapy. In fact, some Authors reported that the increase of IGF-1 to normal values resulted in a reduction of circulating leptin levels [59].

GHD patients suffer from coagulation factors disorders such as the increase of Plasminogen activator inhibitor-1 (PAI) levels, fibrinogen and VIII factor [60-62]. Thrombosis risk is very high, thus further increasing cardiovascular morbidity and mortality risk [61]. Of note, it has been observed that PAI-1 and fibrinogen levels decrease after GH therapy [63] and a normalization of impaired fibrinolysis after treatment of GHD has

been confirmed also in a recent work by Miljic *et al.* [64]. Even the activity of protein S, which is decreased in GHD patients, is normalized by the therapy [65]. In fact, Cakir *et al.* evaluated 19 GHD patients both before and after 6 months of GH replacement therapy [65]. After treatment, a decrease of protein S levels compared to basal and to placebo controls was found in GHD patients; also a reduction of Antithrombin III (ATIII) and C protein was evident. Further studies will be needed in order to evaluate the effectiveness of GH treatment in decreasing cardiovascular risk in GHD. Moreover, it has been shown that values of pregnancy-associated plasma protein A (PAPP-A), a metalloproteinase secreted by artery smooth muscle cells and commonly used as an atherosclerosis marker, are increased in GHD patients compared to healthy controls and are brought within normality range after GH replacement therapy [66]. Even the study by Joaquin *et al.* confirmed the increase of PAPP-A and CRP levels in GHD [66]; that work seems to suggest the existence of a causal mechanism between the reduction of IGF-1 levels and the increase of PAPP-A, also leading to hypothesize that PAPP-A could have a role in the development of atherogenic process of GHD [67] (Fig. 1).

3. Cardiovascular complications

3.a Atherosclerosis

GHD has been associated with an increase of atheromatic plaques in carotid and femoral artery at ultrasonographic evaluation, compared to healthy controls [68, 69]. Other atheromatosis markers in GHD are represented by the increased intima media thickness and by a greater carotid and aortic stiffness [70].

At the beginning of the 2000s, the effect of GHD in the production of nitric oxide (NO) was also evaluated. The decreased systemic synthesis of NO in GHD patients has been demonstrated [71]. This seems to be due to the direct effect of IGF-1 in stimulating NO synthesis in the endothelial cell [72]. In fact, *in vitro* studies demonstrated that endothelial cell has IGF-1 receptors, which are able to directly mediate NO synthesis, thus modulating vessel tone [72]. GHD related IGF-1 decrease is related to a decrease in arterial dilatation and to an increase of platelet aggregation, responsible for the impairment of endothelial and vasodilatatory function [71, 72]. Recently, a study has reported an increase of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NO synthesis, that normalizes after GH therapy [73, 74].

3.b Cardiac function and morphology

Young adults GHD patients have a reduction of left ventricular (LV) mass and ejection fraction and an abnormal diastolic filling pattern. In this regard, some Authors found a significant reduction of LV systolic function as well as a decrease of the posterior wall of LV and of interventricular septum [75]. One open study has evaluated the cardiac function of 14 GHD patients and 12 healthy controls by radionuclide scanning [76]. That study confirmed the reduction of LV ejection fraction and the impairment of cardiac function indexes. The 6 months GH replacement therapy ameliorated cardiac function with a significant improvement in left ventricular ejection fraction (from 53%±9% to 59%±9%, P <0.01) and in cardiac index (from 2.8±0.6 to 3.3±0.8 L/min/m^2, P <0.01). In 2003 a meta-analysis reviewed sixteen trials (9 blinded and 7 open) considering 468 patients who belonged to different populations and who were being treated with different GH dosages and duration of therapy; significant positive effects of GH on cardiac parameters assessed by echocardiography were evident. In particular, LV mass increased by 10.8 (standard deviation: 9.3) g (P=0.02); similarly interventricular septum thickness increased by 0.28 mm (P<0.001) and LV posterior wall by 0.98 mm (P=0.05), confirming the effectiveness of GH replacement therapy on cardiac morphology [77]. Also, Giustina *et al.* demonstrated that GH has acute functional effects on the heart in patients with congestive heart failure (CHF), including both an increase in myocardial contractility and a decrease in vascular resistances, and among patients with CHF, those with low baseline IGF-1 are likely to have fewer beneficial effects from GH infusion [78]. However, a recent study did not show a significant increase of cardiac mass and function at different GH dosages therapies [79].

On the other hand, at cellular level, GH administration seems to improve cardiac function by the IGF-1 mediated calcium-sensitizing effects on myofilaments [80, 81].

3.c Mortality and cardiovascular events in adult GHD

Since the beginning of 1990s, several retrospective studies have demonstrated the relationship between hypopituitarism and the increase of cardiovascular risk, especially in women, with the increase of mortality associated with cardiovascular disease, specifically

cerebrovascular [5, 82-87]. In a study Stochholm *et al.* demonstrated a morbidity increase in GHD, for both sexes, due to several risk factors such as the impaired metabolic profile [88]; recently, a work by van Bunderen *et al*. showed an increase of mortality for cardiovascular diseases in GHD women who were undergoing GH replacement therapy [89]. These data could also suggest that, in women, the association of GHD with an untreated estrogenic deficit could increase the risk of cardiovascular disease and, as a result, mortality [89].

More recent studies have evaluated the association in untreated GHD between the reduced levels of IGF-1 and the presence of coronary calcium deposits [90]. Computed tomography is useful to radiographically identify calcium deposits and has been recently validated as a reliable tool in order to estimate risk of developing coronary disease [91].

On the other hand, data about the impact of GH replacement therapy on the reduction of cardiovascular morbidity and mortality are still lacking. Several works have demonstrated the efficacy of GH replacement therapy in decreasing cardiovascular risk [85, 92, 93], but further controlled clinical trials will be necessary. In view of the worse cardiovascular risk factor and greater mortality of GHD women compared to men [94], the possible sex-related effect of GH replacement therapy on mortality in women has been assessed. Benefits of GH replacement therapy in terms of mortality seemed to be lower than the ones evident in men, probably because lower levels of IGF-1 and lean mass were achieved in women [1]. Hoffman *et al.* demonstrated that hormone therapy in women needs to be specifically titrated and the different response in IGF-1 production results in a lower improvement of lipid profile and fat mass in women than in men [44]. These data show that premenopausal women are somehow resistant to the effects of GH replacement therapy, probably because sex hormones, especially estrogens, can influence the action of GH on IGF-1 production.

4. Remarks

Some peculiar populations require a few specific remarks.

4.a Elderly GHD

The age-related decline of GH/IGF-1 axis activity, also designated as "somatopause", is believed to be involved in the age-associated body composition change, such as decreased lean body, increased body fat and decreased muscle mass, thus mimicking the GHD clinical picture [95]. Mechanisms implicated in this process are mainly represented by changes in hypothalamic neuropeptides and neurotransmitters, leading to decreased GHRH secretion, and somatostatin hypersecretion [95].

Elderly GHD patients usually have a worse cardiovascular risk profile than the younger patients. In fact, two works reported higher prevalence of diabetes mellitus, coronary heart disease, stroke and history of hypertension in older individuals (>65 years) as well as higher values of blood pressure [96, 97]. This is likely explained by the positive correlation of blood pressure, cholesterol and LDL cholesterol levels with age in these patients [96, 97].

In this specific cohort of patients, GH replacement therapy positively and unequivocally affects total and LDL cholesterol levels, whereas it does not improve plasma triglyceride levels [98]. Controversy exists on the effects of the therapy on other cardiovascular risk factors, including insulin, HDL cholesterol, blood pressure and body composition [98]. Only one study evaluated the effects of replacement therapy on cardiac noninvasive structural and functional parameters in elderly GH deficient patients and reported non significant changes after 12 months [99].

4.b GHD after treatment of acromegaly (acroGHD)

GHD may also occur in adults with cured acromegaly [100]. This can happen in some medically treated patients, mainly when pegvisomant is used, or after neurosurgery or irradiation treatment. It can be hypothesized that, in acroGHD, the long-term effects of acromegaly on insulin resistance and hypertension could combine with similar ones from GHD, thus resulting in a further increased cardiovascular risk. Also, the acromegaly-related cardiac abnormalities could worsen after the development of GHD [101]. However, clinical studies do not fully confirm these theoretical hypotheses, as they found a BMI slightly increased [102-104] or, even, similar [105-108] in acroGHD compared to GHD and acromegalic populations. At the same time, while one work reported that acroGHD patients were more hypertensive, dyslipidemic, and diabetic than GHD subjects [109], other Authors pointed out a comparable prevalence of glucose abnormalities and dyslipidemia, as well as a similar amount of body fat and lean mass between acroGHD and ref-

erence GHD groups [110]. It must however be highlighted that Feldt-Rasmussen and colleagues showed that acroGHD patients have a significantly higher prevalence of stroke compared to GHD of other etiologies [111]. As far as GH replacement therapy is concerned, evidence suggests that, in acroGHD, it achieves significant improvements of body composition (mainly body fat), CRP and lipid profile (especially LDL cholesterol) generally after 1 year [101]. However, as Tritos *et al.* found that cardiovascular mortality was increased in the acroGHD group compared with the GHD reference populations [100], a prudent approach is recommended in considering GH replacement in acroGHD patients with elevated cardiovascular risk [101].

5. Safety and cost effectiveness of long-term use of GH therapy

Safety issues related to the long-term use of GH therapy mainly regard the increased frequency of diabetes mellitus and the possible effects on the progression of the underlying tumour causing GHD as well as on de novo neoplasia. However, GH replacement therapy seems to be safe. In fact, prevalence of diabetes mellitus among adult patients with GH replacement seems to be related to classical risk factors for diabetes mellitus, such as BMI and age, and it is probably not increased by GH treatment [112]. As far as the oncological risk is concerned, it does not seem to be increased in the treated subjects [112]. Also, long-term GH replacement in adults is not associated with an additional increased risk of vascular disease and mortality [112].

Recombinant human GH is more expensive than conventional pituitary hormone replacement therapies, such as corticosteroids, sex steroids and thyroxine. However, few data are available on the cost effectiveness of GH replacement therapy. In this regard, hypopituitary patients with untreated GHD have been shown to have a higher cost to society in terms of lost production and medical consumption [113]. Verhelst and colleagues observed a decreased number of sick days after replacement therapy, from 12 days at baseline to 7 days in 6 months of therapy and to 3 days in 24 months of therapy [114]. More recently, a specific study on this subject demonstrated that GH therapy is a cost-effective therapy in Sweden when considering morbidity and mortality associated with GHD and the impact on quality of life [115].

Conclusions

GHD is able to increase cardiovascular risk by influencing the prevalence of well-known risk factors such as central obesity, the impaired lipid and glucose profile and other less-known risk factors such as proinflammatory cytokines, endothelial dysfunction and oxidative stress. Replacement GH therapy has been proven to be beneficial in many studies. However, since available data are limited and not always consistent, the long-term cardiovascular efficacy of GH replacement remains an issue which deserves future attention.

Disclosure

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