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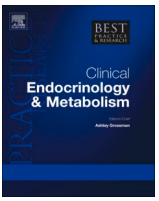

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Dyslipidaemia and growth hormone deficiency – A comprehensive review

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Growth hormone deficiency (GHD) is a common complication of several pituitary and hypothalamic disorders and dependent on the onset of disease. It may have severe clinical implications ranging from growth retardation in childhood-onset, to impaired lipid metabolism and increased cardiovascular risk and mortality in adults. GH effectively modulates lipid metabolism at multiple levels and GHD has been associated with an atherogenic lipid profile, that can be reversed by GH replacement therapy. Despite increasing knowledge on the effects of GH on several key enzymes regulating lipid metabolism and recent breakthroughs in the development and wider availability of recombinant GH preparations, several questions remain regarding the replacement therapy in adults with GHD. This review aims to comprehensively summarize the current knowledge on (i) lipid profile abnormalities in individuals with GHD, (ii) proposed mechanisms of action of GH on lipid and lipoprotein metabolism, and (iii) clinical implications of GH replacement therapy in individuals diagnosed with GHD.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; ApoB, polipoprotein B; BMI, body mass index; C, cholesterol; CE, cholesterol ester; CV, cardiovascular; DBPC/CO, Double-blind placebo-controlled/cross over; FFA, free fatty acids; GH, growth hormone; GHD, growth hormone deficiency; GHRT, growth hormone replacement therapy; HDL, high density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low density lipoprotein; Lpa, lipoprotein (a); LPL, lipoprotein lipase; MTP, microsomal transfer protein; SMR, standard mortality rates; TG, triglycerides; VLDL, (very) low density lipoproteins

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Introduction

Adulthood-onset growth hormone deficiency (GHD) is linked to hypopituitarism (incidence 4–5 cases per 100'000 per year) and is often the first axis affected in hypothalamic-pituitary disorders [1–3]. Childhood-onset GHD is most often idiopathic and isolated. Other causes such as genetic, pituitary and brain tumours and their treatment (surgery and radiotherapy) do exist but are rare [4]. Current guidelines suggest that all patients transitioning to adult care should be reassessed for GH deficiency, as most of these patients will regain normal GH secretion by adulthood [5,6]. However, children with structural lesions of the hypothalamic-pituitary region or genetic causes are more likely to have persistent GHD requiring continued GHRT into adulthood [5].

Over the last few decades, the interest in GH and GH replacement therapy (GHRT) in adults has increased significantly due to two main events: First, the availability of recombinant GH as treatment option since the late 1980 s and second, the publications of two landmark studies reporting poor outcomes of patients with GHD who did not receive GHRT [7,8], with standard mortality rates (SMR) twice as high when compared to individuals under replacement therapy. The poorer outcome was mainly driven by a higher susceptibility of patients with GH deficiency towards cardiovascular events and associated mortality.

Adults with GHD present with a clinical phenotype that is characterized by increased fat mass – predominantly visceral fat – and reduced lean body mass [9]. This phenotype mimics features of the metabolic syndrome with signs of insulin resistance [10] and it is therefore not surprising that dyslipidaemia is a common finding in affected individuals. The dyslipidaemia documented in people with GH deficiency is mainly characterised by elevated total cholesterol and low-density lipoprotein (LDL) levels, both of which are established risk factors for the development of atherosclerotic cardiovascular disease (ASCVD) [11] and may be the underlying cause of the increased mortality observed in hypopituitary patients [12]. Studies have shown that these changes in lipid profiles can be reversed with GHRT [13]. In particular, observational data suggest that patients with hypopituitarism who receive GHRT have a lower mortality rate compared to individuals with those who not receive GHRT [1,14]. It is therefore tempting to speculate that the adverse lipid profile of GHD may be the causal factor for the increased mortality rate in hypopituitarism patients and that GHRT may have the ability to reduce this increased mortality rate to normal levels. However, whether there is a causal relationship between GHRT and these observations is still unclear because of the lack of prospective, placebo-controlled trials with hard clinical endpoints, i.e. major adverse cardiovascular (CV) events or CV-mortality.

This review aims at summarizing the current knowledge of altered lipid metabolism in GHD and the effect of GHRT on lipid profiles in children and adults. We will discuss possible underlying mechanisms and their clinical implications and highlight hot topics with unanswered questions.

Characteristic changes in lipid profile in adults with GHD

In the early 1990 s, Rosén et al. were the first who analysed the lipid profiles of more than 100 adults with established GHD and compared them with those of healthy controls from the general population [15]. In these early studies, they observed that GHD patients had significantly higher plasma triglycerides and lower HDL cholesterol (HDL-C) levels, the typical dyslipidaemia of patients with the metabolic syndrome and consistent with the observed increase in total visceral fat mass in GHD patients. Further studies followed, confirming the documented dyslipidaemic state in adults with both childhood-onset and adult-onset GHD but these studies mainly reported elevated levels of total cholesterol (TC) and LDL cholesterol (LDL-C) compared with age-, sex- and BMI-matched controls or with predicted age-adjusted reference ranges [16,17].

However, other hormonal deficiencies must also be considered when interpreting lipid profiles in patients with hypopituitarism. As other pituitary deficiencies such as thyrotrophin with thyroxin, corticotrophin with cortisol and the gonadal axis also influence lipid metabolism, it is sometimes difficult to distinguish between GHD-mediated dyslipidaemia and inappropriate replacement therapy of other pituitary axes. Against this background, studies investigating lipid profiles in patients with isolated GHD are of particular interest. Soares Barreto-Filho et al. [18], de Boer et al. [16] and Abs et al. [19] compared patients with isolated GHD with age-, sex- and BMI-matched controls. While Soares Barreto-Filho et al.

included GHD patients with a mutated GHRH receptor [18], de Boer H et al. studied only men to avoid possible confounding by the different effects of sex steroids on lipid metabolism [16]. The results of Abs et al. were derived from the post-marketing KIMS database and included isolated GHD of various aetiologies [19]. All these studies consistently documented a modest increase in TC and LDL-C, whereas TG and HDL-C were not altered compared with the respective control population. These important findings suggest that adult GHD is indeed associated with a lipid profile known to be associated with premature ASCVD.

Influence of clinical characteristics on lipid profiles of adults with GHD

The KIMS post-marketing database allowed analysis of several baseline demographic and clinical parameters on lipid profiles in individuals with adult GHD [19] (Table 1).

Sex

Female patients had higher TC levels than men by around 0.2 mmol/L, with no difference between premenopausal and postmenopausal women. The observed sex difference in TC was mainly due to higher HDL-C concentrations of 0.2 mmol/L in female patients [19].

Age

As seen in the general population, there was a steady increase in TC levels from 5.0 mmol/L among 20–30 years old to around 6.1 mmol/L among individuals aged 40–49 years, and beyond. The increase in TC with age was mainly driven by a steady increase in LDL-C, while HDL-C remained constant with increasing age. Likewise, TGs also increased with age, but stabilised in a similar pattern to TC concentrations [19].

Clinical parameters

Other parameters associated with pituitary disease as age at onset of GHD, duration of GHD, underlying aetiology, severity of hypopituitarism (number of hormonal axes affected), waist circumference, body mass index (BMI) and history of cerebral radiotherapy were not associated with significant changes in the lipid profiles of GHD patients [19].

Effects of GHRT on lipid profiles in adults with GHD

A number of controlled clinical trials in adults with GHD have investigated the effect of GHRT on the lipid profile (Table 2). Although a few studies reported no significant effects of GHRT on the lipid profile [20,21], the majority of studies – comprehensively summarised in a meta-analysis by Maison et al. [22] – showed a rather small (5–10%) but significant treatment-related reduction in TC, mainly due to a reduction in LDL-C [22]. These findings were confirmed in the large uncontrolled post-marketing KIMS

Table 1
Lipid and Lipoprotein Profiles in Adults with GH-Deficiency.

Author	Year	n	TC	TG	HDL-C	LDL-C	Notes
Rosen T	1993	104 (MO)	⇔	⇑	⇓		Population-based normal controls (WHO MONICA study)
de Boer H	1994	64 (CO)	⇑	⇔	⇔	⇑	age and sex matched control group
Attanasio A	1997	74 (CO)	⇑		⇓ (CO)	⇑ (CO)	compared with reference range
		99 (AO)	⇑		⇓ (AO)	⇑ (AO)	

n = number of patients, TC = total cholesterol, TG = triglycerides, HDL-C = HDL-cholesterol, LDL-C = LDL-cholesterol, ApoB = apolipoprotein B, CO = childhood-onset GH-deficiency, AO = adulthood-onset GH-deficiency, MO = mixed-onset GH-deficiency, ⇑, ⇓ denotes statistically significant increase/decrease vs controls, ⇔ denotes no significant change.

database. While the effects of GHRT on TC and LDL-C levels are well established, there is less consistent evidence for effects on TG and HDL-C, and changes did not reach statistical significance [22].

Effects of long-acting GH replacement on lipid profiles

Several long-acting formulations of GH have been developed in order to improve patient adherence, particularly in the paediatric patient population. Such formulations allow the frequency of GH injections to be reduced from daily to weekly or even monthly [23]. Randomised controlled clinical trials of some long-acting GH preparations have reported non-inferiority when compared to daily recombinant GH in terms of growth induction, effects on body composition and IGF-1 levels in children and young adults with GHD [23]. It is, therefore likely that the metabolic effects on TC and LDL-C will be similar. However, formal assessment of the effect long-acting GH preparations on lipid profile is still lacking to our knowledge.

Factors influencing the effects of GHRT on lipid profiles in adults with GHD

Sex

Provided an adequate dose of GHRT was administered, male and female patients showed similar patterns of lipid profile changes following GHRT [19].

Age

There was no difference in the effects of GHRT on lipid profiles with age. In fact, elderly patients with GHD (> 65 years of age) showed a similar response to GHRT as seen in younger individuals [24].

Duration of treatment

Most controlled trials were conducted over a period of 6–12 months [22] and showed a 5–10% reduction in TC and LDL-C concentrations compared to placebo. The KIMS post-marketing database, which provides data beyond one year of follow-up, shows that improvements in TC and LDL-C concentrations were greatest in the first year of treatment. The effects were largely maintained in subsequent years, with only marginal additional improvements [19]. These effects were also seen in patients who were already on statins, suggesting additional beneficial effects of GHRT on lipid metabolism [25].

Table 2
Effects of GH Replacement Therapy on Lipid and Lipoprotein Profiles in Adults with GHD.

Author	Year	n	Design	Duration (months)	TC	TG	HDL-C	LDL-C
Salomon F	1989	24 (MO)	DBPC	6	⇓	⇔	⇔	⇓
Whitehead H	1992	14 (MO)	DBPC/CO	6	⇔	⇔	⇔	⇔
Eden S	1993	9 (AO)	DBPC/CO	6	⇔	⇔	⇑	⇔
Russell-Jones DL	1994	18 (MO)	DBPC	2	⇓	⇔	⇔	⇓
Beshyah SA	1995	20 (MO)	DBPC	6	⇔	⇔	⇔	⇔
Weaver JU	1995	22 (MO)	DBPC	6	⇓	⇔		
Attanasio A	1997	74 (CO) 99 (AO)	DBPC	6	(CO) ⇔ (AO) ⇓		(CO) ⇑ (AO) ⇑	(CO) ⇔ (AO) ⇓
Cuneo R	1998	166 (MO)	DBPC	6	⇓		⇔	⇓

DBPC/CO = Double-blind placebo-controlled/cross over, n = number of patients, TC = total cholesterol, TG = triglyceride, HDL-C = HDL-cholesterol, LDL-C = LDL cholesterol, ApoB = apolipoprotein B, ApoA = apolipoprotein A, CO = childhood-onset GH-deficiency, AO = adulthood-onset GH-deficiency, MO = mixed-onset GH-deficiency. ⇑ / ⇓ / ⇔ denotes increased, decreased and unchanged concentrations, respectively, in patients with adult GH-deficiency following GH replacement therapy.

Aetiology of GHD

Irrespective of the underlying condition responsible for GHD (i.e. craniopharyngioma, childhood-onset, adulthood-onset, isolated GHD or multiple pituitary deficiencies, irradiation, apoplexy (Sheehan's syndrome)), GHRT consistently reduced TC and LDL-C concentrations and to a similar extent [26–31].

Effects of GHRT on lipid profiles in children and adolescents with GHD

GHRT is a standard treatment option to promote linear growth in children and adolescents with GHD. As mentioned above, growth per se represents an extreme situation of anabolism and thus GH exerts profound metabolic effects on protein and lipid metabolism [32] leading to the established changes in body composition, bone mineral density and lipid profile [22,33,34]. Impaired lipid metabolism in children with GHD may contribute to an increased risk of cardiovascular morbidity and mortality in adulthood [12,35]. Indeed, the available evidence on the origins of ASCVD in healthy children and young adults suggests that the development of atheromatous plaques begins early in childhood during the prepubertal years [36].

Although less well studied in children, altered lipid profiles characterised by elevated levels of TC and LDL-C have also been reported, as seen in adult patients with GHD. In contrast to adults, most studies report an additional increase in TG and a decrease in HDL-C concentrations when compared to matched controls [37–42]. The latter constellation of dyslipidaemia mimics the characteristic changes that can be seen in individuals with the metabolic syndrome and has therefore been observed typically in young individuals with GHD and concomitant obesity (e.g. hypothalamic obesity in patients with craniopharyngioma) [37].

In addition, current evidence suggests that short-term and long-term GHRT have beneficial effects on the lipid profile of children, mainly with reductions in TC and LDL-C [35,37–39,41–44]. Interestingly, most investigators also report a decrease in TG and an increase in HDL-C concentrations after short-term and long-term GHRT in children [38].

The same findings have been reported in adolescents with GHD, with the addition of prolonged elevations in postprandial TG levels. There is considerable evidence for a positive correlation between postprandial TG exposure after oral lipid load and carotid and coronary atherosclerosis [45,46] and this may be another pathophysiological mechanism by which GHD may increase the susceptibility to ASCVD.

Lipid profiles of individuals with GHD with vs. without GHRT in the transition period

Recent guidelines recommend that GHRT treatment should be continued until the final height is reached and resumed as early as possible after confirming adult GHD in patients with childhood-onset GHD [47]. However, prolonged interruption of GHRT in the transitional period between childhood and adulthood is frequently observed because of the cost of treatment or lack of compliance. There is limited data on the metabolic derangements in patients with childhood-onset GHD [48] and the adverse effects of prolonged treatment interruption in adolescents and young adults [49]. The main findings of these studies indicate that lipid profiles often worsen with increases in TC, LDL-C and TG and decreases in HDL-C levels during GH cessation [50–54], yet these changes reverse when GHRT is resumed [49,50,55]. However, other studies could not confirm the favourable effects of GHRT on lipid profiles in the transition period [56–58]. This might be related to small sample sizes [56], different durations of follow-up or the rather heterogeneous nature of childhood-onset GHD.

Proposed mechanisms of action of GH on lipid and lipoprotein metabolism

Critical to understanding dyslipidaemia is the fact that lipids are bound to lipoproteins. The function of these lipoproteins is to solubilise lipids in the circulation and interact with enzymes and receptors to transport both exogenously digested, absorbed and endogenously produced lipids (i.e. TG, cholesterol) to peripheral tissues for fuel (i.e. skeletal, cardiac muscle) or storage (i.e. adipose tissue) [59]. It is therefore essential to assess the effects of GH on the metabolism of key lipoproteins to fully understand the effect of GHRT on the lipid profile.

Apolipoprotein B100 (apoB) is a protein required for the synthesis and hepatic secretion of very low-density lipoproteins (VLDL). Each VLDL particle contains an apoB lipoprotein that is conserved during conversion to IDL and eventually to LDL[60]. The lipid profile is therefore largely dependent on the secretion and clearance rate of apoB-containing lipoproteins (VLDL, IDL, LDL). Since VLDL apoB is the precursor of IDL and LDL apoB, and since hepatic overproduction of VLDL apoB has been implicated in a number of hyperlipidaemic disorders known to be associated with premature ASCVD [61,62], understanding VLDL apoB kinetics is of particular importance. On the other hand, the metabolic pathways of HDL are more complex. As GH has not been shown to have a significant effect on HDL metabolism, we will not further discuss HDL metabolism here.

Many in vitro and in vivo studies have suggested that the regulation of apoB secretion is post-translational and that increased availability of intrahepatic lipid substrates (i.e. TGs and cholesterol) is critical to stimulate VLDL apoB secretion [63,64]. A possible regulatory effect of GH should therefore be discussed in the light of its effects on intrahepatic substrate availability. Alternatively, GH may regulate VLDL apoB secretion via the microsomal transfer protein (MTP). MTP targets lipid transfer within the rough endoplasmic reticulum and prevents degradation of apoB, thereby enhancing VLDL apoB secretion [65]. Experimental data from rats suggest that MTP expression (mRNA and protein) is sexually dimorphic and is regulated by the sexually dimorphic secretory pattern of GH [65]. In contrast, the clearance of lipoproteins involves a complex interaction between enzymes (lipoprotein lipase, LPL; hepatic lipase, HL) and receptors (LDL receptor, LDL receptor related protein, VLDL receptor) [66]. Changes in the clearance rate of a lipoprotein fraction are therefore likely to be associated with a change in the enzyme activity and/or the number or activity of the corresponding receptor.

The known effects of GH on receptors and enzymes involved in lipoprotein metabolism are summarised in Fig. 1. GH is a potent lipolytic hormone, acting on peripheral adipose tissue resulting in a decrease in body fat mass – one of the most consistent findings after GHRT – and an increase in free fatty acids (FFA) flux to the liver [22,67]. FFA can be esterified to triglycerides (TG) or cholesterol esters (CE), thereby increasing intrahepatic lipid substrate availability. This results in an increase in VLDL apoB secretion, thereby removing lipids from the liver and transporting them to peripheral tissues for use or storage. In addition, in vitro and in vivo data suggest that GH upregulates hepatic LDL receptors in normal cells [68], in hepG2 cells [69], in rats [70] and in humans [71]. This is likely to result in increased uptake of apoB-containing lipoproteins, particularly LDL-C[72]. The core lipids of these lipoproteins may (i) re-stimulate VLDL apoB secretion by increasing intrahepatic substrate availability and (ii) reduce endogenous cholesterol synthesis by inhibiting the key rate-limiting enzyme HMG-CoA reductase [73]. Consistent with this hypothesis, plasma mevalonic acid concentrations, a reliable surrogate marker of endogenous cholesterol synthesis [74], have been shown to decrease following GH replacement therapy [13].

Cholesterol 7-alpha-hydroxylase (C7αOH) is the main enzyme that controls the conversion of cholesterol to bile acids. This enzyme controls the excretion of cholesterol via the enterohepatic pathway. GH treatment in children has been shown to increase hepatic bile synthesis [75], which is consistent with experimental data showing increased activity of C7αOH after GHRT in hypophysectomised rats [76]. The possible regulatory effect of GH on bile acid metabolism is of particular interest, as both GH secretion [77] and bile acid synthesis [78] decline in parallel with increasing age. It is reasonable to assume that these two age-related changes may be interrelated.

Studies investigating the effect of GH on lipoprotein lipase (LPL) and hepatic lipase (HL) activity – the enzymes that hydrolyse the TG within apoB-containing lipoproteins – have yielded conflicting results. In hypophysectomised rats, LPL and HL activity have been shown to increase after GH treatment [79], whereas in humans, GH has been associated with a decreased total post-heparine LPL activity [80] or had no effect on LPL activity at all [81]. However, LPL activity in human adipose tissue decreased after GH therapy in obese women [82] and in GH-deficient adults [81]. In contrast, postheparine HL activity increased in one study [81], but decreased after initiation of GHRT in adults [80]. Small sample sizes of the studies, and the different and rather sophisticated techniques used to measure the activities of these enzymes may explain these conflicting findings.

In addition, although measurements of plasma lipid provide concentrations provide useful information, they cannot identify any mechanism for abnormalities of these concentrations. The transport

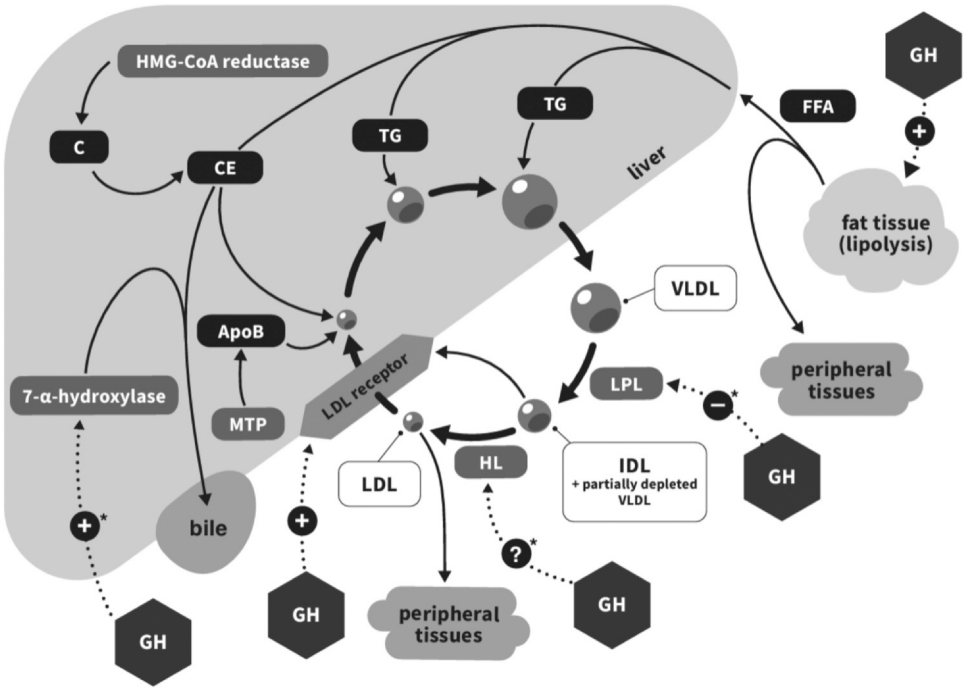

Fig. 1. GH exerts its lipolytic action on fat tissue resulting in an increase of free fatty acid (FFA) flux towards the liver. FFA can be esterified to triglycerides (TG) or cholesterol-ester (CE) thereby enhancing intrahepatic lipid substrate availability which, in turn, stimulate VLDL apoB secretion. Microsomal triglyceride transfer protein (MTP) targets lipid transfer within the rough endoplasmatic reticulum and prevents degradation of apoB. GH upregulates hepatic LDL receptor. Consequently, an increased uptake of partially TG depleted VLDL, IDL and LDL is likely to occur. The core lipids of these lipoproteins may (i) stimulate again VLDL apo-secretion and (ii) reduce endogenous cholesterol synthesis by inhibiting the key enzyme HMG-CoA reductase. Increased excretion of cholesterol via the bile acid pathway is possible through the stimulation of the key enzyme for bile acid synthesis, 7-alpha-hydroxylase. Human adipose tissue lipoprotein lipase (LPL) activity is reduced after GH. The available data on the effect of GH on total postheparin LPL and hepatic lipase activity is conflicting. * indicates uncertain effects of GH. Abbreviations: ApoB, apolipoprotein B; C, cholesterol; CE, cholesterol ester; FFA, free fatty acids; GH, growth hormone; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; MTP, microsomal transfer protein; TG, triglycerides; VLDL, very-low-density lipoprotein.

of lipids is in a constant flux. A plasma lipid concentration is a function of two opposing processes, synthesis and clearance. An elevated concentration may be due to increased synthesis or decreased clearance, or a combination of both. Advances in the use of stable isotopes have made it possible to measure lipoprotein kinetics in humans. By administering a constant infusion of the stable isotope ^{13}C-leucine and measuring the incorporation of this labelled amino acid into the individual apoB molecule/lipoprotein using gas chromatography-mass spectrometry, apoB kinetic parameters (secretion and clearance rate) can be estimated. This method led to the following key findings in patients with GHD before and after GHRT:

1) Patients with GHD have an increased hepatic secretion rate and decreased catabolism of VLDL apoB compared to age-, sex- and BMI-matched controls [83]. Two factors may explain these findings: (i) the insulin resistant state and (ii) the downregulation of LDL receptor expression in GH-deficient patients. Insulin resistance is associated with decreased activity of LPL [84], which may contribute to decreased clearance of VLDL particles in peripheral tissues, as evidenced by a decreased catabolic rate in this study. As a result, the plasma VLDL pool increases and the VLDL particles are then taken up by

the liver, increasing the size of the intrahepatic lipid pool, which in turn stimulates the VLDL apoB secretion rate, consistent with the findings of a study in patients with non-insulin-dependent diabetes mellitus [85]. A reduction in LDL receptor function may contribute to (i) impaired catabolism of VLDL apoB, since direct hepatic removal of partially degraded VLDL is mediated by the LDL receptor, and (ii) an increase in endogenous cholesterol synthesis [83]. An increased intrahepatic cholesterol pool derived from endogenous synthesis may in turn lead to increased VLDL apoB secretion.

2) Physiological GHRT further increases VLDL apoB secretion and reverses the reduced VLDL apoB clearance rate [86]. Based on previous considerations, it is likely that the increase in VLDL apoB secretion rate is related to the lipolytic action of GH. Indeed, GH replacement therapy results in a mean reduction in fat mass [22,67]. The increase in VLDL apoB removal is probably related to an increase in hepatic uptake of partially delipidated VLDL particles via the LDL receptor pathway, thereby reducing the rate of conversion of VLDL to LDL. This would be consistent with the reduction in LDL-C concentrations as observed in several studies [22,67].
3) Compared with age-, sex- and BMI-matched controls, individuals with GHD have an overall reduced turnover as characterised by a decrease in LDL apoB production and clearance rate [87]. The reduced clearance is most likely due to reduced availability of the hepatic LDL receptor, whereas the reduced LDL apoB production rate is intriguing. A possible mechanism could be a decrease in the activity of enzymes involved in the conversion of VLDL-IDL-LDL particles, such as lipoprotein lipase and hepatic lipases. However, measurements of the activity of these enzymes are controversial and the effects on GH are still unclear and may be tissue specific [88–90].
4) Consistent with previous findings, a controlled stable isotope study showed that GHRT in adults with GHD led to a reduction in LDL-C concentrations, which was associated with an increase in LDL apoB clearance, without changing the LDL apoB production rate. This is most likely due to an increase in LDL receptor expression [91].

Many of the effects of GH are thought to be mediated by insulin-like growth factor-1 (IGF-1). IGF-I has been shown to decrease VLDL apoB, suggesting decreased VLDL apoB secretion and/or increased VLDL apoB clearance in normolipidaemic subjects [92], in patients with non-insulin-dependent diabetes mellitus [93], and in individuals with insulin-dependent diabetes mellitus [33]. However, none of these findings were consistent with the increased VLDL apoB secretion and clearance observed after GHRT. Furthermore, studies in rats suggest that IGF-I does not affect the expression of the hepatic LDL receptor [94]. It is therefore conceivable that the effects on lipoproteins are largely due to direct effects of GH.

Quality of lipoproteins: Small dense LDLs in adults with GHD and the effect of GHRT

In addition to the quantitative effects of increased LDL particle concentrations, the quality of LDL particles has been shown to be important for the associated atherogenicity [95]. LDL comprises several distinct subclasses that differ in size, density, metabolic behaviour and atherogenicity, with at least four major subspecies as assessed by peak particle diameter or ultracentrifugal density [95,96]. Individuals generally fall into two broad subgroups, the majority with a predominance of larger or medium-sized LDL and a minority with a higher proportion of smaller LDL particles [97]. LDL size appears to be an important predictor of cardiovascular events and progression to coronary heart disease (CHD) [95,98].

Data on small dense LDL in patients with GHD are scarce. Current data in a small sample of patients suggest that patients with GHD do not have increased small dense LDL and that short-term GHRT has no significant effect on fasting [99] or postprandial small dense LDL concentrations [100].

Lipoprotein(a) in GHD and the effect of GHRT

Lipoprotein(a) (LP(a)) is similar to LDL but has an additional apolipoprotein (apo(a)) covalently linked to it which, in turn, is a member of the plasminogen gene superfamily [101]. There is a remarkable genetic variation in its length, which explains the inherited differences in apo(a) molecular mass and

therefore the wide range of Lp(a) concentrations seen in different individuals [101]. Epidemiological evidence suggests that it is an independent risk factor for the development of atherosclerosis [102,103].

Although genetic factors appear to account for most of the variance in Lp(a) concentrations, studies suggest that hormones may be involved in modulating Lp(a) levels. GHRT has been shown to be associated with increased Lp(a) concentrations in five studies [15,104–107], whereas they remained unchanged in two others [13,108]. In contrast, IGF-I therapy has been shown to reduce Lp(a) in normal subjects [109], in patients with Laron syndrome [107] and in patients with non-insulin-dependent diabetes mellitus [93]. It is therefore tempting to speculate that insulin sensitivity is a key player in the modulation of Lp(a) levels, since GHRT, especially with higher doses, decreases insulin sensitivity [110–112], whereas IGF-I has been shown to improve it [92]. However, the pathophysiological background and the relevance of these observations with regard to the pathogenesis of ASCVD remain unclear.

Clinical implications of GHRT on cardiovascular morbidity and mortality

Surrogate markers of early atherosclerotic disease, such as carotid intima-media thickness or endothelial function have been shown to be impaired in both adulthood-onset [35] and childhood-onset GHD [37]. Notably, several studies have reported improvements in these surrogate markers with GHRT [35,37,86,113,114], suggesting a beneficial effect of GHRT on endothelium and possibly leading to a reduction in the risk of ASCVD.

However, prospective randomised placebo-controlled trials with clinical endpoints of cardiovascular morbidity or mortality are still lacking. There is only indirect evidence from post-marketing studies indicating that early morphological and functional atherosclerotic changes in the carotid arteries of children with GHD improve with GHRT and that elevated cardiovascular risk estimates normalise in adult patients with continued GHRT [115]. These improved cardiovascular risk estimates are largely driven by reductions in TC and LDL-C and to some extent by reductions in high-sensitivity C-reactive protein (hsCRP; low-grade inflammation) levels which is also considered as an important factor in the pathophysiology of atheroslcerosis [116].

Summary and conclusions

GH appears to play a central role in hepatic lipoprotein metabolism; but we are currently only at the beginning to understand the multitude of direct and indirect mechanisms involved. Adult GHD is often associated with dyslipidaemia, particularly elevated TC and LDL-C concentrations, which may increase the risk of ASCVD. Increased VLDL apoB secretion and reduced hepatic VLDL apoB clearance rates may partly explain the altered lipid profile observed in these patients. GH replacement therapy may have beneficial effects on the lipid profile by increasing direct hepatic removal of VLDL apoB, thereby reducing its conversion to LDL. In addition, it is likely that GH treatment leads to increased hepatic removal of LDL. Although GHRT has been shown to further stimulate VLDL apoB secretion, this effect is largely outweighed by a strong GH-mediated upregulation of hepatic LDL receptors. Several unresolved questions remain: (i) the underlying mechanisms behind the changes in HDL concentrations with GHRT, (ii) the contribution of thyroid dysfunction and other hormonal deficiencies in adults with GH deficiency [67] to the observed changes in lipoprotein metabolism, and (iii) the effects of GH on other important factors that regulate VLDL apoB secretion, such as microsomal triglyceride transfer protein [117].

Despite the increasing knowledge of metabolic changes due to GHD and the effects of GHRT, it is still unclear whether altered lipid metabolism is the main cause of the increased risk of ASCVD and, more importantly for patients, whether GHRT could reduce cardiovascular mortality. Therefore, mechanistic studies are also needed to investigate the effects of GH on other lipoprotein classes before and after GHRT and most importantly, clinical trials investigating the long-term effects of GHRT on the rate of major adverse cardiovascular endpoints and associated mortality are urgently needed to establish future guidelines.

Research agenda

- Mechanistic studies aiming at investigation the effect of GH on other lipoproteins such as HDLs.
- Prospective controlled trials investigating the respective role of GHRT, but also of other pituitary deficiencies (i.e. TSH, ACTH) in the context of lipid metabolism.
- Clinical trials investigating the long-term effects of GHRT on the rate of major adverse cardiovascular endpoints and associated mortality

Practice points

- Adult GHD is associated with dyslipidaemia, particularly elevated TC and LDL-C concentrations,
- Childhood-onset of GHD is also associated with dyslipidemia characterised by increased TC and LDL-C but also TG and decreased HDL-C concentrations
- GHRT consistently reduces TC and LDL-C concentrations in adults and children
- Direct effects on hepatic LDL-receptors and bile acid metabolism and indirect effects through the lipolytic action on peripheral tissues – thereby increasing hepatic lipid substrate availability - are the proposed pathophysiological mechanisms
- Dyslipidemia may contribute to the increased risk of atherosclerotic diseases in hypopituitary patients with GHD
- Whether GHRT results in a reduction in cardiovascular morbidity and mortality in patients with hypopituitarism remains to be established

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Declaration of Competing Interest

FE and MH do not have any conflict of interest. EC has received speakers' honoraria, consulting fees from Novo Nordisk and Pfizer. EC was supported by a Pfizer for an investigator-initiated research.

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