GROWTH HORMONE DEFICIENCY IN ADULTS

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ABSTRACT: Adults with Growth hormone (GH) deficiency is now being recognised to display many distinct clinical, metabolic and psychological abnormalities. It has been demonstrated that GH deficient (GHD) adults display features of multiple insulin resistant syndrome (MIRS) which predispose the GHD adults to increased cardiovascular morbidity and mortality. These features include central obesity, insulin resistance and glucose intolerance, hypertension, dyslipidaemia that includes a reduced level of high density lipoprotein cholesterol, an elevated triglyceride level and small low density lipoprotein cholesterol size. Furthermore, GHD adults are found to have a lower bone mass and a reduced sense of well-being.

Replacement of GH in these GHD adults has brought about a major improvement in psychological well-being and central obesity. The improvement of some of the lipid abnormalities is however more modest. Insulin resistance, the corner stone of MIRS, is however not altered by GH replacement. Long term data is as yet unavailable to assess if GH replacement reduces cardiovascular mortality and morbidity in these subjects. *(JUMMEC 1999; 2: 74-80)*

KEYWORDS: Growth hormone, Hormone deficiency, Diabetes mellitus, Central obesity, Hyperlipidaemia, Hypertension.

Introduction

Growth hormone (GH) deficiency in childhood are characterised by short stature, delayed bone maturation, excess adiposity with a predominant truncal distribution, reduced lean body mass and fasting hypoglycaemia, all of which are improved or normalised with GH treatment (1).

The incidence of pituitary insufficiency is not fully known and is found not only in patients with pituitary or parapituitary tumours but also in those who has been exposed to previous radiation, the field of which includes the pituitary for example head and neck malignancies, nasopharyngeal carcinoma and cranial irradiation for brain tumour or childhood leukaemia. Traditionally, adults with hypopituitarism are only replaced with sex steroids, corticosteroids and thyroxine where clinically indicated, although GH deficiency is common in these patients (2). However, GH deficiency in adults also represents a specific clinical syndrome characterised by a wide range of clinical features as reviewed by Cuneo et al (3) and more recently by us (4).

Overall mortality was found to be two fold higher in hypopituitary patients than in the general population,

despite appropriate conventional hormone replacement, largely accountable for by an increase in mortality from cardiovascular disease (2,5). This increase tended to be more prominent in women (2,5). This may be due to the similarity between the metabolic aberrations associated with GH deficiency and Multiple Insulin Resistance Syndrome (MIRS) (4) and is discussed below.

Cardiovascular system

The increased cardiovascular mortality is supported by the findings of increased atherosclerotic plaques in the carotid arteries (6), reduced aortic distensibility (7) and ischaemic-like electrocardiographic ST segment changes on exercise testing in GH deficient (GHD) adults (8). Hypertension is also found to be more common in GHD and hypopituitary adults (9,10), which is in keeping with the premature atherosclerosis found in these patients. GH replacement has resulted in a reduction in the diastolic blood pressure in the GHD adults although no data is available on long term cardiovascular morbidity and mortality to date (4).

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Fibrinogen and plasminogen activator inhibitor-1 (PAI-1), fibrinolytic factors that are also independent athero-genic risk factors for cardiovascular disease, are found to be higher in GHD adults compared with matched healthy controls (11). This observation further supports the atherogenic tendencies in GHD adults. The elevated PAI-1 level decreases after 2 years of GH replacement, but the fibrinogen levels remain high (12).

However, the role of GH in the regulation of cardiac function is not fully defined. Dilated cardiomyopathy is associated with GH deficiency (13). An increase in left ventricular mass, stroke volume and cardiac output, and a reduced peripheral vascular resistance has been documented in GHD adults given GH replacement therapy (13). Interestingly, even GH sufficient adults with idiopathic dilated cardiomyopathy seem to respond positively to GH therapy (14). However, this is yet to be confirmed in a controlled trial to establish GH as an effective therapeutic agent in patients with idiopathic dilated cardiomyopathy.

Body composition

GHD adults have an increased fat mass (FM) and a reduced fat free mass (FFM) compared to healthy subjects matched for age, sex and body mass index (BMI) (15, 16). The increase in waist circumference and waist to hip ratio (WHR) (15, 16) suggests that the increased adiposity found in GHD adults is centrally distributed. This was confirmed independently, using dual energy X-ray absorptiometry (DEXA) (17), and magnetic resonance imaging (16). Importantly, visceral fat is ~ 30 - 35% higher in the GHD adults compared to the controls whereas subcutaneous fat is only ~ 11% higher (16). This visceral fat, which is metabolically more active, may be responsible for the metabolic abnormalities found in both GH deficiency (4) and MIRS (18). This visceral fat is also more prominent in the female GHD adults compared to their male counterparts (16), the significance of which will be discussed in Section VI.

There have been numerous studies documenting the beneficial effect of GH on reducing FM and increasing FFM in GHD adults (4, 19). These changes tend to be GH dose dependent (4, 17). The reduction in whole body FM in GHD adults in GHD adults receiving GH replacement is mainly due to a marked decrease in central or visceral fat in GHD subjects, as determined by change in WHR (17, 20) and DEXA (17, 21). Furthermore, these body compositional changes induced by GH are more pronounced for young, lean male subjects (12, 21, 22), and appear to be more pronounced in subjects with adult onset rather than childhood onset GH deficiency (23). This reduction in central obesity should potentially reduce the increased cardiovascular risk of GH deficiency in adults, especially those with adult onset disease.

Muscle strength

The reduced FFM found in GHD adults results in a mild to moderate reduction in muscle strength concordant with the reduction in muscle mass (19). The increase in FFM induced by GH replacement therapy is more evident in the limbs (4, 21). This corresponds with an increase in quadriceps isometric muscle strength following 12 or more months of treatment (19). Similar improvements are also seen in exercise capacity (19).

Insulin resistance

A. Insulin sensitivity in GH deficiency

Hypopituitary and GHD adults are traditionally thought to be insulin sensitive (24). Most of these early data were derived from animal studies and were supported by the observation of fasting hypoglycaemia in children with GH deficiency which was normalised following GH replacement therapy (25). However when insulin sensitivity was measured by the glucose decay rate obtained during an insulin tolerance test, GHD children were not more insulin sensitive than normal children (26). Subsequently, Bougneres and co-workers (27) demonstrated a diminished hepatic glycogen store in untreated hypopituitary children which might have accounted for the proneness to spontaneous fasting hypoglycaemia in hypopituitary children.

Fasting glucose was not found to be different between hypopituitary GHD adults and matched control subjects (3, 28, 29). Cuneo and co workers noticed a higher fasting insulin level in obese GHD adults, suggestive of insulin resistance in these subjects (3). Furthermore, Beshyah et al demonstrated that the prevalence of abnormal glucose tolerance was higher in GHD hypopituitary adults (44%) than in a control group (21%)(28) and was accompanied by insulin resistance in the GHD adults. GH is known to increase insulin secretion directly. Theoretically, it is possible that GH deficiency may reduce the capacity of the β cell to respond to the insulin resistant state and maintain glucose tolerance, as supported by the increased prevalence of abnormal glucose tolerance when glucose tolerance was formally tested (28). However, despite the foregoing discussion, retrospective epidemiological studies have not demonstrated an increased prevalence of diabetes mellitus in GHD adults (9, 10).

Using a variety of measurements, a significant and major reduction in whole body insulin sensitivity was demonstrated in GHD adults (17, 25, 29, 30). It must be noted that the GHD adults in the studies were overweight with mean BMI ranging from 26.4 to 28.5 kg/m². It is interesting to note that the insulin resistance was related only to the degree of GH deficiency and not to the number of pituitary hormones that were defi-

cient (25). In a subsequent study, we found that, whilst glucose turnover and partitioning of whole body glucose utilisation into the glycolytic flux (GF) and glucose storage (GS) pathways were normal in GHD adults basally, insulin activation of glucose uptake in the periphery was markedly decreased, and that this insulin resistance was due primarily to a reduction in insulin stimulated exogenous GS (29). This was closely associated with a major defect in the insulin activation of muscle glycogen synthase (GlySyn), the rate limiting enzyme for GS (29). The insulin resistance increased in severity with the duration of GH deficiency and was associated with alterations in fasting TG levels, insulin levels and abdominal obesity, thereby closely resembling the abnormalities seen in MIRS (29). In fact, the degree of reduction in the insulin activated Rd, GS and GlySyn found in GHD adults (29) was similar to that seen in obese and NIDDM subjects (31).

The mechanisms responsible for the peripheral insulin resistance in GHD adults are not entirely clear but a key contributor must be the markedly reduced GlySyn in GHD adults. The increased visceral FM present in GHD adults (16) may serve as a depot for increased FFA flux (18), thereby raising FFA levels which in turn induce insulin resistance. It is probable that an altered Randle-FFA cycle might have contributed to the decreased insulin sensitivity, particularly in the GS pathway (25). Alternatively, there are data to support a direct influence of FFA on cellular membrane structure with possible alterations to insulin receptor binding and in vivo insulin action (25). The latter mechanism would support a hypothesis that the influence of FFA on muscle GlySyn insulin occurs at an earlier step in the insulin signal transduction cadence, such as insulin receptor or kinase activation (20, 25).

IGF-I levels have been shown to reflect basal GH secretion in hypopituitary and normal subjects (32). The observed positive correlation between IGF-I levels and insulin sensitivity in GHD adults (29) suggests that the impaired basal GH secretion may be an aetiological factor in the insulin resistant state, similar to that described for obese subjects (33). In addition, IGF-I levels are closely linked to the duration of GH deficiency and this would support our observation of a significant relationship between the duration of GH deficiency and impaired insulin action (29). Thus, it seems likely that the duration and the severity of GH deficiency are important in the development of the insulin resistant state found in GHD adults (25, 29). Therefore it can be hypothesised that GH deficiency leads to central obesity, which in turn serves as a depot for an increased FFA flux that induces insulin resistance through the Randle cycle of substrate competition.

Despite the profound insulin resistance described above, pancreatic β cell function is found to be impaired (25,

30). This may explain the increased incidence of impaired glucose tolerance in GHD adults (28).

B. The effect of GH replacement

In acromegaly and GH treated children and adults, a decrease in insulin sensitivity has been demonstrated (29). Weaver et al (17) reported an increase in both the fasting glucose and insulin levels after 6 months of GH replacement indicating a deterioration in insulin resistance. However, this deterioration in insulin sensitivity is only transient and with longer duration of GH replacement, most studies have demonstrated a return of insulin sensitivity back to the level prior to GH replacement (23, 25). The transient raised level of FFA with GH replacement also implicates FFA in the mechanism of GH-induced insulin resistance, certainly in the short term (25). This occurred despite a significant sustained reduction in abdominal FM. The partitioning of total body glucose disposal into the two major intracellular pathways of glucose metabolism namely, glycolysis and glucose storage, and the activities of glycogen synthase were unchanged by GH replacement therapy (23).

The impact of GH therapy in GH deficiency on b cell function is not entirely clear. The earlier studies in b cell function assessment (17, 25) following GH therapy generally indicate increased insulin responses to oral glucose. This is not unexpected given the persistence or even worsening of the insulin resistance with GH therapy (see above). The net impact of the continuing insulin resistance in these GH treated GHD adults on overall carbohydrate tolerance in the long term is uncertain, although the majority of studies have not found a deterioration of glucose tolerance (25, 34).

In summary, long term GH replacement in GHD adults has resulted in a slight reduction or no change of insulin sensitivity in these subjects despite the favourable effects on body composition, especially the reduction of abdominal obesity. The reason for the persistence of the insulin resistance is not known but may be related to the chronic GH-induced alterations of FFA metabolism.

Lipid abnormality

A. Growth hormone deficiency

GH has been shown to be important for the normal expression of LDL receptors in rat liver (35). Numerous recent studies have documented alterations in serum lipids and lipoproteins in hypopituitary and GHD adults, although no apparent uniformity in the lipid abnormalities has been observed. Hypercholesterolaemia and hypertriglyceridaemia associated with elevated low density lipoprotein (LDL) and reduced high density lipoprotein (HDL) cholesterol levels have been described

(4). De Boer and co-workers (15) also found that both the total and LDL cholesterol levels were higher in those with multiple pituitary hormone deficiency than those with isolated GH deficiency. The subjects with multiple pituitary hormone deficiencies in the study were more GH deficient as assessed by IGF-I and maximum GH response to stimulation tests. Thus, it is probable that GH secretory status and possibly duration of GH deficiency have an impact on total and LDL cholesterol. The inverse relationship demonstrated between IGF-I and LDL cholesterol levels further support this contention (15). It seems that the degree of hypercholesterolaemia found in hypopituitary and GHD adults is mild (9, 15, 28). De Boer and co workers found that only patients with severe GH deficiency have an increased risk of developing clinically relevant hypercholesterolaemia (15). In addition, O'Neal and coworkers showed that in GHD subjects the lipid abnormality is associated with smaller, denser LDL particles (36). Thus the increased cardiovascular mortality found in long standing hypopituitary subjects on conventional replacement therapy (2) is due not only to the altered lipid levels but also to a higher prevalence of small, dense LDL particle (36) which are highly atherogenic.

The lipid abnormalities noted above seem to be more prominent in female than male subjects (9, 28, 36). The similar WHR in the female and male GHD adults (11, 36) indicates a comparative higher central fat distribution in the female GHD adults and would support the observation of a more atherogenic lipid profile in female subjects (9, 28, 36). In addition, a higher prevalence of glucose intolerance (28) and mortality rate (2, 3) were found in the female GHD adults. In NIDDM, females also have a relatively greater excess risk of cardiovascular disease than their male counterparts (37), perhaps reflecting the more adverse effect of glucose intolerance on lipids and lipoproteins, including LDL size in women (38). Importantly, both GH deficiency and NIDDM are characterised by insulin resistance and a similar dyslipidaemic pattern, including small dense LDL particles. Thus, the expected positive effect of female gender and oestrogen supplementation on lipid profiles and cardiovascular risk in female GHD adults is blunted (36).

Obesity, especially abdominal obesity, is associated with increased TG and LDL cholesterol levels, and a reduced HDL cholesterol level in healthy and NIDDM subjects (39). Abdominal obesity is also present in GHD adults and as discussed above may account for a similar lipid profile abnormality in GHD adults. Nevertheless, it is important to note that in pituitary sufficient individuals, small LDL particle size is also associated with insulin resistance (40). A similar association has been also demonstrated in GHD adults (36) which further supports the hypothesis that patients with GH

deficiency and MIRS have similar pathophysiology.

B. The effect of GH replacement therapy

A reduction in total and LDL cholesterol levels in GHD adults receiving GH replacement was found in some but not all studies (4). It has been noted that a greater reduction in total and LDL cholesterol was seen in those subjects with higher pretreatment levels (41). A GH dose dependent effect, as seen on body composition changes, was not seen on changes in total and LDL cholesterol levels. Hypertriglyceridaemia, a common abnormality in GHD adults, was not found to be significantly improved by GH replacement, although normalisation of the TG levels in GHD adults with high pre treatment TG levels was observed in one study (42). As expected, the LDL size did not change with GH replacement (21).

Lp(a) was found to be elevated after GH replacement in a time and dose dependent manner (4). This is supported by the high Lp(a) levels found in acromegaly and in normal healthy subject undergoing GH therapy (4). On the other hand, no increase in Lp(a) was demonstrated after 2 months of GH replacement in GHD adults (43). The lack of concordance in the findings of the studies may be due to the fact that the increase in Lp(a) is not found in all the GHD adults undergoing GH replacement, for example 6 out of 21 subjects in one study (41). These data are therefore consistent with the view that Lp(a) response to GH replacement is determined by genetic factors, and thus only 'susceptible' subjects will adversely respond to GH replacement therapy.

In summary, GH replacement in GHD adults results in a decrease in total and LDL cholesterol levels, especially in those individuals with high pretreatment levels. Dramatic improvement in HDL cholesterol levels is less certain. The atherogenic small, dense LDL particle size associated with GHD adults does not appear to be altered by GH replacement. Finally, Lp(a), an independent cardiovascular risk factor, seems to increase in some subjects in a GH dose- and time-dependent manner. It is therefore premature to conclude that GH replacement in GHD adults has a net benefit with respect to the total in vivo lipid profile, and longer term studies of the impact of GH on cardiovascular morbidity and mortality are required in GHD adults.

Bone mass

Reduced bone mass has been documented in adults with GH deficiency, particularly in those with adult onset disease, as supported by epidemiological evidence of an increased fracture rate (19). GH replacement increases bone turnover, but continuous therapy for at least 12 months is needed before an increase in bone mass is observed. The important question is whether

the increased rate of osteoporotic fractures observed in GHD adults can be reduced with GH replacement. So far no such data is available.

Psychological well-being

Decreased psychological well-being has been reported in GHD adults (3, 19). GHD adults have been reported to have less energy, greater emotional lability, more difficulties with sexual relationships, and a greater sense of social isolation (19). In double blind controlled trials, GH replacement was found to improve mood and energy levels. This improvement in psychological well being has now become one of the main indications for GH replacement in GHD adults.

Conclusion

GH deficiency in adults is associated with alterations of body composition, psychological well-being and metabolic disturbances characterised by insulin resistance; dyslipidaemia which includes a decreased HDL cholesterol, increased TG levels and the prevalence of small, dense LDL particles; an increased incidence of carbohydrate intolerance and risk of future ischaemic heart disease, all features of MIRS. The central feature of this syndrome, insulin resistance, was found to be related to both the severity and duration of GH deficiency, and to serum TG levels (29). It is unclear at this point as to why GHD adults display such a close resemblance to patients with MIRS.

Given the protean metabolic effects of GH and the clear relationship between the features of GH deficiency, and duration and severity of GH deficiency, GH replacement therapy should improve the features of GH deficiency in adults. The improvement in lipid parameters in GHD adults is more evident with higher doses of GH, but there is little or no change in other metabolic features. Increasingly, there is a move towards using a lower dose of GH due to a lower side effect profile. Certainly, this lower dose of GH replacement has resulted in a reduction in the metabolically active abdominal fat on the one hand but an increase in Lp(a) on the other. The insulin resistant state found in GHD adults may worsen with GH replacement, even at the lower doses (17, 21). Thus, there may be only a small overall net positive impact on the features of MIRS by GH replacement therapy in GHD adults. However, this does not compromise the subjective and objective improvement in sense of well being and energy perceived by many GHD subjects on GH replacement (3, 19). Nevertheless, the dose and route of administration of GH may confound the true physiologic impact of GH replacement therapy on various metabolic parameters as the GH profile is far from physiological in subcutaneous GH injection as compared to the normal pulsatile

GH secretion. Future studies will need to define the appropriate GH dose, optimal duration of therapy, metabolic effect of physiologic pulsatile GH versus subcutaneous GH administration and thus the route of GH administration. More recently, using a much more sensitive assay, it has been demonstrated that far from being absolutely GH deficient, GHD subjects are able to secrete GH at smaller amplitudes (Toogood *et al,* 1998). Thus, GH secretagogue is being investigated to see if these agents can be used to augment the attenuated GH secretion. These agents are certainly more convenient to use as they can be administered orally, unlike GH which like all the peptide hormones has to be given parenterally. Intense research is now underway to assess if these agents can alleviate the features of GH deficiency more physiologically and therefore with less side effects.

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