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Growth Hormone Therapy and its Relationship to Insulin Resistance, Glucose Intolerance and Diabetes Mellitus

A Review of Recent Evidence

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Abstract

It is widely recommended that consideration should be given to the therapeutic use of growth hormone (GH) in adults with GH deficiency, whether the condition is of childhood or adult onset. One reason for this recommendation is the possibility that such treatment may reduce the excess cardiovascular risk which is associated with hypopituitarism. This excess risk has been well documented, with mortality ratios of 1.7 to 2.2 being quoted in different studies, and may be a result of the insulin resistance which occurs in hypopituitarism. However, it has also been suggested that this insulin resistance may itself be the result of GH deficiency, especially as GH deficiency is accompanied by suggestive morphological features such as central adiposity. There is, however, no direct evidence that the increase in cardiovascular risk in hypopituitarism is the result of GH deficiency, and the only prospective study designed to examine the relationship failed to find a statistically significant correlation between the two. Since GH administration may also have an independent adverse effect on insulin sensitivity and could thus cause a theoretical worsening of cardiovascular risk, it is important to review the observed effects of GH administration on carbohydrate metabolism in practice.

Interpretation of the literature is made difficult by many confounding factors, including differences in study duration, biochemical tools adopted, the use of selected populations and the dose-dependent effect of GH on synthesis of insulin-like growth factor-1. One of the most sensitive markers of a deterioration in insulin sensitivity is the serum insulin level. A rise in serum insulin (fasting, or post-glucose load) was reported in all studies in which it was measured. The majority of studies have also reported a rise in fasting blood glucose. A smaller proportion of reports noted an associated increase in postprandial glucose and in glycosylated haemoglobin (HbA_{1c}) while a few reported new cases of either impaired glucose tolerance or frank diabetes mellitus. In general, however, the observed deterioration in insulin sensitivity was small and increases which occurred in blood glucose were small. Nevertheless, these data indicate that rather than lead to an improvement in insulin resistance in hypopituitarism, GH treatment may actually make it worse. As it is also known that even minor reductions in insulin sensitivity may be associated with a clinically significant increase in cardiovascular risk, further large-scale controlled trials are required before the efficacy and safety of GH treatment of adults can be established.

1. Insulin Resistance, Glucose Intolerance, Diabetes Mellitus and the Risk of Cardiovascular Disease

It is well established that growth hormone (GH) antagonises some actions of insulin. The excessive secretion of GH in acromegaly is associated with an increased incidence of both diabetes mellitus and vascular disease, and there are abundant data on the effects of administered GH, especially at higher doses.[1,2] Hence, it has been suspected that the therapeutic administration of GH might have similar adverse effects, even at the lower doses more generally used today. Since GH was first ad-

ministered to children over 40 years ago[3] and to adults in the mid 1980s, the accumulated experience of its use is considerable. Although many workers have reported evidence of adverse effects of GH on carbohydrate metabolism, these effects are not generally thought to be clinically important. However, the publication of two recent reports from major databases has highlighted a small excess of new cases of diabetes mellitus in young people treated with GH.[4,5] A greatly increased prevalence of diabetes mellitus has also been reported in a study of young people who had had a bone marrow transplant for malignant disease, some of whom had also received GH treatment.[6] It is therefore appropriate to review the effects of the therapeutic use of GH on carbohydrate metabolism.

Before considering the evidence for an effect of GH on blood glucose in clinical practice, it is necessary to review some of the complex interrelationships which exist between insulin, glucose and cardiovascular risk, as well as the multiple confounding issues which make assessment of the published literature difficult.

1.1 Insulin Resistance

Diabetes mellitus is associated with an increased risk of cardiovascular disease, which is generally thought to be related to the degree of hyperglycaemia. However, the hyperglycaemia of type 2 diabetes mellitus is to a considerable extent the result of systemic resistance to the action of insulin, and it is now believed that insulin resistance is itself an independent factor conferring an increased risk of vascular disease.[7,8] This effect of insulin resistance is likely to be mediated by a complex interaction of many different metabolic factors which include hyperglycaemia, hyperlipidaemia and a direct effect of hyperinsulinaemia on atherogenesis. Whatever the mechanism, it is apparent that any assessment of the effect of GH on carbohydrate metabolism should at the very least include measures of insulin resistance as well as of blood glucose.

1.1.1 Actions of Insulin

Insulin normally stimulates glucose uptake by the liver, as well as hepatic glycogenesis. Glycogen breakdown and gluconeogenesis are inhibited, resulting in a fall in hepatic glucose output (HGO). Insulin also stimulates glucose uptake and phosphorylation in skeletal muscle, with associated muscle glycogenesis. It stimulates lipogenesis and inhibits lipolysis and release of free fatty acids (FFAs).

1.1.2 Metabolic Features of Insulin Resistance

Resistance to the action of insulin is therefore reflected in an increase in blood glucose; which is the result of both increased synthesis and reduced clearance. Insulin resistance is also reflected by an increase in circulating FFAs, as well as fasting triglyceride concentrations and decreased synthesis of high-density lipoprotein. Such resistance also leads, through loss of feedback, to increased secretion of insulin (and connecting peptide, or C-peptide, which is co-secreted with insulin on an equimolar basis) by the pancreas. If pancreatic insulin reserve is normal, then hyperinsulinaemia (both fasting and postprandial) will follow. If, however, insulin resistance is associated with any reduction in pancreatic reserve, the extent of hyperinsulinaemia may be less marked. It is also relevant that both glucose and increased circulating FFAs may themselves have an adverse effect on insulin secretion.

1.2 Glucose Intolerance and Diabetes Mellitus

1.2.1 Defects in Glucose Synthesis and Glucose Utilisation

If insulin secretion is defective, or is insufficient to overcome peripheral resistance to its action, hyperglycaemia will result. If this is associated with a significant increase in HGO, fasting plasma glucose will be elevated, but if the predominant defect is decreased glucose utilisation, fasting glucose may be normal whereas postprandial levels are high. The criteria recently recommended by the American Diabetes Association (ADA) for the diagnosis of diabetes and 'impaired fasting glu-

cose' (IFG) are based entirely on the fasting plasma glucose level and will not therefore detect the cases in which the dominant defect is one of glucose utilisation. This contrasts with the WHO criteria for diagnosis, which rely on both the fasting and 2-hour values in an oral glucose tolerance test. A 2-hour value of >11.1 mmol/L is (when confirmed) diagnostic of diabetes, while a value of between 7.8 and 11.1 mmol/L represents 'impaired glucose tolerance' (IGT). Only about 50% of cases of IGT have IFG, and would therefore be classified as normal by ADA criteria.[9] Neither IFG nor IGT are clinical entities, but whereas the former is regarded as a risk category for future diabetes mellitus, the latter is a risk category for both future diabetes mellitus and cardiovascular disease.

1.2.2 Impaired Glucose Tolerance and Cardiovascular Disease

The criteria adopted for the diagnosis of diabetes mellitus (as opposed to glucose intolerance) are based on the observation that there is a threshold above which there is a steep rise in the incidence of microvascular complications, such as diabetic retinopathy and nephropathy. There is, however, little evidence of a similar threshold associated with a rise in the risk of macrovascular (cardiovascular, cerebrovascular and peripheral vascular) diseases. Indeed, there is a linear relationship between cardiovascular risk and the height of the blood glucose level in IGT, and yet it follows that reliance solely on the concentration of fasting glucose may miss a substantial proportion of those whose insulin resistance is sufficient to cause an increase in cardiovascular risk.[10,11] Furthermore, there is now good evidence that cardiovascular risk correlates not only with categories of glucose intolerance, but also with changing concentrations of glucose within the normal range.[12,13]

1.3 Predisposition to the Development of Insulin Resistance and Hyperglycaemia

The pathogenesis of type 2 diabetes mellitus is extraordinarily complex, and is based on the inheritance of multiple genetic factors which tend to predispose to either defective insulin action, or secretion, or both.[14,15] The expression of this predisposition is enhanced by advancing age, as well as by other factors with an adverse effect on either insulin secretion (e.g. unrelated disease of the pancreas) or insulin action (including pregnancy, obesity, hyperlipidaemia, reduced bulk or reduced use of skeletal muscle, unrelated disease such as thyrotoxicosis, hepatic disease, and treatment with drugs such as glucocorticoids). It follows that a factor with the potential to cause an adverse effect on insulin action may express it only in those with an independent predisposition to insulin resistance. This obviously applies to conditions such as pregnancy and obesity, but it would also apply to treatment with GH. It follows that if GH is shown to have even a small mean effect on carbohydrate metabolism in cohort studies, it may be predicted that this would nevertheless be sufficient to cause clinically significant hyperglycaemia in the minority who were otherwise at risk. It should not be forgotten, however, that the evidence available today suggests that even small changes in glucose tolerance may also be harmful.[12]

1.4 Markers of Insulin Resistance, Glucose Intolerance and Diabetes Mellitus

A large number of different markers of insulin resistance can be used in clinical research and routine clinical practice (table I). The reference methods for use in research are measures of glucose production and disposal using euglycaemic and hyperinsulinaemic clamp techniques. However, other measures include indices of insulin sensitivity determined during either a frequently sampled intravenous glucose test or an insulin suppression test. These techniques are labour-intensive and for this reason simpler methods are adopted when studying large cohorts, or for surveillance in routine clinical practice. Such simpler methods include the responses of glucose and/or insulin to an oral glucose load, determined as 2-hour concentration, area under the curve (AUC) or the sum of discrete values, as well as measurement of fasting glucose and insulin. In this respect fasting glucose

Table I. Markers of insulin resistance

Serum insulin
Fasting insulin (and/or C-peptide)
AUC for insulin (or C-peptide) following OGTT
Insulin responses during an IVGTT
Assessment of insulin sensitivity (S_I) indices during an FSIGT or other dynamic tests
Glucose
Fasting blood glucose
2-hour glucose after OGTT
AUC glucose during OGTT
HbA_{1c} as a marker of ambient glucose over the preceding 6 weeks
Fructosamine as a marker of ambient glucose over the preceding 2 to 3 weeks
Clinical diabetes mellitus
Glucose and insulin
A measure of insulin resistance, HOMA can be derived from the fasting concentrations of insulin and glucose
Lipids
Fasting hypertriglyceridaemia
Increased free fatty acids
Reduced high-density lipoprotein
Other markers
In experimental situations, the effect of insulin on glucose synthesis and disposal can be determined using hyperinsulinaemic and euglycaemic clamps

AUC = area under the curve; **FSIGT** = frequently sampled intravenous glucose test; **HbA_{1c}** = glycosylated haemoglobin; **HOMA** = homeostatic model of assessment; **IVGTT** = intravenous glucose tolerance test; **OGTT** = oral glucose tolerance test.

is relatively less, and fasting insulin relatively more, sensitive.

Once insulin resistance is marked, the patient will develop more overt degrees of hyperglycaemia provided there is some associated impairment of secretion or action. If plasma glucose exceeds 7.0 mmol/L in the fasting state (ADA, WHO) or 11.1 mmol/L after a glucose load (WHO), the diagnosis of diabetes mellitus may be made. Higher mean blood glucose concentrations are also associated with progressive elevation in the percentage of glycosylated haemoglobin (HbA_{1c}) or glycosylated plasma protein (fructosamine). A rise in either of the last two markers would be expected only if there were more persistent elevations in ambient glucose levels.

2. Insulin Resistance and Cardiovascular Risk in Hypopituitarism

The issue is made more complex by the fact that the condition for which GH is usually prescribed, hypopituitarism, is also associated with reduced insulin sensitivity and, in all probability, an increased incidence of cardiovascular death.[16,17] It follows that although GH is antagonistic to some actions of insulin, its use in the management of hypopituitarism could conceivably be associated with some reduction in pre-existing risk.[18]

2.1 Hypopituitarism and Mortality

2.1.1 Children

Disease of the hypothalamus and pituitary in childhood is associated with a greatly increased mortality, but mainly because of the effect of the primary disease, especially craniopharyngioma, possibly related largely to suboptimal management of corticotropin and antidiuretic hormone deficiency.[19-21] The same is true for children rendered GH deficient by treatment of unrelated malignant disease. Insufficient data are yet available to determine whether children and adolescents with other causes of growth delay (including both those with GH deficiency and those without) have an increase in long-term mortality.

2.1.2 Adults

Pituitary disease in adults is also associated with increased mortality, even when those with independent causes of increased cardiovascular risk (e.g. acromegaly and Cushing's disease) are excluded. This excess is thought to be the result of hypopituitarism. Rosen and Bengtsson[22] reported an overall standardised mortality ratio (SMR) of 1.8 in 333 patients managed for pituitary disease between 1956 and 1987. The risk appeared to be the result of increased cardiovascular disease (SMR 1.9), and was more pronounced in women.

Three further retrospective studies have reported similar overall findings, with differences in detail. In a review of 172 patients with defined

hypopituitarism who were managed between 1967 and 1994, Bates et al.[23] reported an all-cause SMR of 1.7 (women 2.3 *vs* men 1.5), but no significant increase in deaths from vascular disease. They also noted that the presence of hypogonadism (both treated and untreated) seemed to be associated with improved survival. When they extended their observations to a population of 349 managed between 1968 and 1992 the differences were less marked, with an overall SMR of 1.3, with no gender difference and no excess in cardiovascular disease.[24] Bülow et al.[25] reported on 344 patients who had had surgery for pituitary disease in a single centre between 1946 and 1988. They found an overall SMR of 2.2 (women 2.9 *vs* men 1.9), with coronary vascular disease contributing to mortality (SMR 1.6) but with the greatest excess being in cerebrovascular disease (SMR 3.4; women 4.9 *vs* men 2.6).

Most recently the British group have reported the results of an 8-year prospective study of 1014 patients in the West Midlands area.[26] The increased mortality was confirmed (SMR 1.9), especially in women (SMR 2.3 *vs* men 1.6). Cardiovascular (SMR 1.8) and cerebrovascular (SMR 2.4) diseases were both increased, but the greatest excess was in respiratory disorders (SMR 2.7). Multiple regression analysis confirmed both gender and a primary diagnosis of craniopharyngioma as independent predictors of increased mortality. They also found that untreated hypogonadism carried a worse prognosis, which conflicted to some extent with earlier findings from the same area.[23]

2.2 Growth Hormone Deficiency, Insulin Resistance and Increased Mortality in Adults with Hypopituitarism

The majority of those observed in the above studies on hypopituitarism would have had GH deficiency, and as all were receiving orthodox treatment for associated deficiencies in corticotropin and thyroid-stimulating hormone (but not always for luteinising hormone/follicle-stimulating hormone) it has been plausibly suggested that GH deficiency might be a significant factor. This led to the evolution of the concept of a GH deficiency syndrome of which one aspect was an increase in cardiovascular mortality.[27] This was supported by the observation that those with GH deficiency had some of the phenotypic features of the insulin resistance syndrome; [7] increased total fat mass, with central adiposity, reduced lean body mass and unfavourable lipid profile, as well as other evidence of accelerated macrovascular disease.[28]

Although suggestive, the concept that the increased mortality of hypopituitarism is largely the result of GH deficiency remains hypothetical. Indeed, Tomlinson and colleagues[26] could find no evidence for an association between GH deficiency and mortality in their prospective study of hypopituitarism. Nevertheless, it is possible that a proportion of the insulin resistance and cardiovascular risk of hypopituitarism is the result of GH deficiency, even though many other factors may be involved. Such factors include the nature of the underlying disease and the extent and precision with which other hormone deficiencies are replaced. The role of untreated gonadotropin deficiency has been highlighted by Tomlinson et al.,[26] who also observed that the majority of older female patients do not receive replacement therapy with sex steroids. Such nontreatment might underlie the previously observed effect of gender on mortality,[22,23,25] and it may be relevant that GH (and, by implication, GH deficiency) modifies the metabolism of other hormone replacement therapy.[29]

On the other hand, there is evidence to support the suggestion that GH deficiency is involved, at least in part, and numerous groups have shown that the introduction of GH replacement therapy is associated with a reduction in central adiposity and an increase in lean body mass, changes that would be expected to improve insulin sensitivity.[16-18]

If, however, GH deficiency was the dominant factor leading to insulin resistance in hypopituitarism, it would be predicted that the introduction of GH replacement therapy would lead to a clear and consistent improvement in markers of insulin resistance. The fact that this is not the case, and that most available evidence shows either no change or

an actual deterioration in insulin sensitivity, indicates either that the contribution made by GH deficiency to the insulin resistance of hypopituitarism is small, or that any benefit which accompanies the introduction of GH treatment is outweighed by independent adverse effects of the hormone on other aspects of carbohydrate metabolism.

3. Other Factors Confounding Interpretation of the Literature

A number of other confounding factors must be considered before reviewing the observed effects of GH treatment in clinical practice.

3.1 Growth Hormone and Insulin-Like Growth Factor-1

GH stimulates the synthesis of insulin-like growth factor-1 (IGF1), leading to increased concentrations both in the circulation and in peripheral tissues. IGF1 shares some of the metabolic actions of GH, and it is not clear to what extent both are metabolically active and how much GH simply serves as prohormone. However, IGF1 also interacts to some extent with the insulin receptor and it follows that some of its actions are insulin-like, rather than insulin antagonistic. Hence, it becomes difficult to predict the detailed consequences of GH treatment, which will cause increases both in circulating GH and in IGF1 synthesis. Mauras and colleagues[30] have investigated this potential paradox by comparing the effects of administering either GH or IGF1 for 8 weeks to patients with severe GH deficiency. In brief, they observed that although the effects of the two on fat mass and protein anabolism were qualitatively similar, their effects on carbohydrate metabolism were divergent. Both resulted in an increase in HGO, but GH was associated with a rise in the circulating concentrations of both insulin and blood glucose, whereas IGF1 was not. They also reported conceptually similar results in a study of eight individuals with GH receptor deficiency (Laron-type dwarfism) in which IGF1 concentrations are low but GH is normal or high.[31] In this second study they observed that the administration of IGF1 resulted in an increase in HGO, but a fall in serum insulin and no change in glucose. The experimental blockade of the GH receptor in normal volunteers with pegvisomant leads to a fall in IGF1, but not GH, and is associated with some deterioration in insulin sensitivity in the nonfasting state.[32]

3.2 Different Study Populations

Because of the differential actions of GH and IGF1 on carbohydrate metabolism, it is possible that some of the variation observed between the results of different clinical studies is partly the result of differences in baseline concentrations of the two hormones. Thus, studies in children and adolescents include those with GH deficiency and those who have had GH treatment for growth delay but who have had normal GH reserve. Estimation of GH reserve is also notoriously difficult in adolescence, and it is well recognised that a percentage of those defined as being GH deficient in youth will be found to have normal reserve when retested as adults. Similarly, the effects of GH on a prepubertal child will change when the child starts to mature, since puberty is itself characterised by increasing insulin resistance.

Studies in adults also include mixed populations (table II). They include those with childhood-onset disease (both isolated, idiopathic GH deficiency and structural disease of the hypothalamus and pituitary) and those with adult-onset disease (usually the result of a pituitary adenoma and its treatment). Those with childhood-onset disease tend to have lower levels of circulating IGF1, while a percentage of patients with adult-onset GH deficiency have IGF1 levels that lie within the reference range.[33] Insulin resistance is very much more common in some racial groups, as well as in the elderly, and this also contributes to the heterogeneity observed in published work.

Comparison between studies is also made difficult by the fact that the doses of GH used in children tend to be higher than in adults. Those used in childhood are calculated in proportion to body size and clinical response, while those used in adulthood are titrated against serum IGF1. Finally,

Table II. Populations which may be included for study of the effects of growth hormone (GH)

Children with childhood-onset GH deficiency (COCHD)
Idiopathic isolated GH deficiency
GH deficiency caused by destructive disease of the hypothalamus/pituitary and/or its treatment
GH deficiency caused by treatment given for some other disease, such as whole body irradiation for malignancy of the bone marrow
GH deficiency caused by head injury
GH deficiency associated with congenital defects with independent risk of glucose intolerance, such as Prader-Willi syndrome
Other children treated with GH
Idiopathic growth delay with normal GH reserve
Congenital disorders associated with short stature but with normal GH reserve, and which may have an independent risk of glucose intolerance, such as Turner's syndrome
Adults with COGHD
A heterogeneous group, reflecting the different causes of COGHD (see above)
Adults with adult-onset GH deficiency
GH deficiency caused by destructive disease of the hypothalamus/pituitary and/or its treatment
GH deficiency caused by treatment given for some other disease, such as whole body irradiation for malignancy of the bone marrow
GH deficiency caused by head injury
Idiopathic GH deficiency, including those treated for the normal decline of GH secretion in later life

some conditions treated with GH in childhood have an independent risk of glucose intolerance and diabetes and include both those who are GH deficient (e.g. Prader-Willi syndrome) and those who are not (e.g. Turner's syndrome).

3.3 Population Selection

One other important aspect of population selection needs to be considered, especially in long-term observational studies in GH-treated cohorts. This is the withdrawal of any individual who develops hyperglycaemia which is judged to be clinically significant. The majority of the long-term observational studies on the use of GH are extensions of earlier short-term, randomised comparisons with placebo, and at least some of these report that participants who developed hyperglycaemia in the early stages were withdrawn from the study. This needs to be remembered when the authors extend their observations over succeeding years and compare, for example, mean fasting blood glucose at the beginning and end of their observation period. Even if the data are paired, they may be invalidated by exclusion of affected individuals.

4. Effect of Growth Hormone on Carbohydrate Metabolism

It was anticipated that despite the known antagonistic effects of GH on insulin sensitivity, its use in GH deficiency might result in a demonstrable beneficial effect. However, it became apparent from early studies (reviewed elsewhere)[16,17,34] that if GH had any beneficial effect, it was slight and most observers reported some degree of worsening of insulin sensitivity or glucose intolerance. It is possible that this was partly the result of using larger doses of GH in adulthood, instead of titrating the GH dose against the serum IGF1 levels as is the current recommended practice.[35,36] However, this is not a factor in more recent studies.

4.1 Effect of Growth Hormone Treatment on Fasting Insulin Level

Weaver and colleagues[37] found that fasting insulin levels rose in their 12-month study of 22 adults with GH deficiency, as did Beshyah et al.[38] in an 18-month study of 11 out of a cohort of 38 adults, published at the same time. This finding would have been more pronounced if two of the original cohort had not been withdrawn earlier because they had developed glucose intolerance. Indeed, the subsequent reports by this same group have to be interpreted in the light of sequential population selection. A total of 5 of their 38 patients developed glucose intolerance in the first 18 months and seem to have been excluded from consideration in subsequent publications. Despite this, the reports of long-term outcome of the truncated cohort still demonstrated significant increases in fasting insulin at 4 years[39] and in the AUC for insulin after a glucose load at 7 years.[40]

Elevation of fasting insulin was also observed in four further studies (both open and controlled) of the use of GH for 24, 3, 4 and 30 months in, respectively, 11,[41] 18,[42] 24[43] and 11[44] adults with GH deficiency. Mauras and colleagues[30] also observed an increase in fasting insulin in a study of eight young people in which the effects of low- and high-dose GH were compared.

Studies in young people have shown that fasting insulin levels rise significantly after the administration of GH, and this elevation is maintained for at least 3[45] and 4[46] years. It has also been long established that the withdrawal of GH in young people is associated with a fall in insulin levels,[47] and this was confirmed more recently.[48] In another study of 18 individuals with childhood onset GH deficiency, there was no change in fasting insulin after GH withdrawal but there was a marked rise when it was reintroduced.[49]

Other major studies which have considered the safety profile of administered GH have made no reference to the measurement of fasting insulin.[35,36,50-52] This is also true of the large industry-coordinated database studies.[53-56]

4.2 Other Studies of Insulin Sensitivity

There have been a number of studies of the effect of GH (or GH withdrawal) on insulin sensitivity, and these have used a variety of different techniques, including calculation of homeostatic model of assessment (HOMA) status, insulin response to oral and intravenous glucose loads, and hyperinsulinaemic and euglycaemic clamp studies. The general conclusion from the majority is that the administration of GH, even in small and titrated doses, is associated with evidence of a significant deterioration in insulin sensitivity.[37,41,43-46,49]

There has, however, been one study that reported contrasting results. Hwu et al.[57] used a modified insulin suppression test (involving combined infusions of insulin, glucose and somatostatin) to study changes in insulin sensitivity in 21 GH-deficient adults before and after a 12-month part-controlled, part-open study of GH treatment. The main finding was that the introduction of GH was associated with evidence of normalisation of insulin resistance. There is no clear explanation for the discrepancy between these findings and those of the majority of other groups, unless it relates to the pretreatment body mass index (BMI) of the study population. The magnitude of GH-mediated changes in insulin sensitivity has been shown to correlate with adiposity,[37] and the individuals studied by Hwu and colleagues were noticeably slim (mean BMI 22.6 kg/m^2) compared with those in other published work.

4.3 Effect of Growth Hormone on Fasting Blood Glucose

As noted above for measurements of insulin, a number of relevant studies make no reference to the effects of GH on fasting blood glucose.[33,35,42,50,54,55] The findings of those that do are variable. Thus, a rise in fasting plasma glucose was observed in 166 patients followed for 12 months,[52] 25 followed for 12 months,[38] 22 followed for 12 months,[37] 24 followed for 4 months,[43] 8 followed for 2 months,[30] and 90 followed for 6 months.[51] Chipman and colleagues[56] also reported a rise in fasting glucose in two large multicentre studies (67 adults with childhood-onset GH deficiency and 98 with adult-onset GH deficiency). Vahl et al.[58] reported a rise in fasting glucose following reintroduction of GH replacement therapy in childhood-onset GH deficiency.

Others have demonstrated rises in fasting plasma glucose which were not, however, reported to be statistically significant. Thus, Chrisoulidou et al.[40] reported a rise of mean fasting plasma glucose in their 7-year study of a selected population from 4.9 ± 0.4 (SD) to 5.2 ± 0.7 mmol/L. Similarly, Seminara et al.[45] reported a rise in fasting plasma glucose from 4.7 ± 0.1 (SEM) to 5.0 ± 0.1 mmol/L over 36 months. Fasting glucose rose in the 24 patients followed up for 24 months by Florakis et al.[51] from 4.78 ± 0.1 (SEM) to 5.44 ± 0.41 mmol/L.

The elevation in fasting glucose observed in two studies was noted to be transient. Al-Shoumer and colleagues[39] reported an increase in fasting

glucose at 12 months in 13 individuals, but this was not sustained (even though fasting insulin remained clearly elevated). Very similar results were reported more recently by Christopher et al.[41] in their detailed analysis of changes of insulin sensitivity in 11 individuals treated with GH for 2 years.

However, other groups have failed to detect any change in fasting glucose. Plasma levels remained unchanged in both the high- and low-dose groups followed up by Mauras et al.[30] for 6 months or more. Other studies of childhood-onset GH deficiency reported that plasma glucose remained constant,[45,46] even though each noted a rise in fasting insulin. Rosenfalck et al.[44] also found in their 30-month study of 11 adults with GH deficiency that glucose remained constant while other measures indicated a significant deterioration in insulin sensitivity. No change in fasting glucose was observed in one other small, open 3-month study.[59]

4.4 Effect of Growth Hormone on Post-Prandial Glucose and Other Measures of Glucose Tolerance

No changes in the AUC for glucose were observed in two studies from one centre,[39,40] even though small but significant rises had earlier been reported by the same group.[38] Others have also reported significant elevation in postprandial glucose.[43-45] On the other hand, Saenger et al.[46] found that the AUC for glucose was unchanged after 5 years' treatment of childhood-onset GH deficiency.

4.5 Effect of Growth Hormone on Glycosylated Haemoglobin

Sustained elevation in plasma glucose is reflected in a rise in HbA_{1c} even within the normal range. When Beshyah and Johnston[17] reviewed the literature in 1999, they found that of seven studies which examined changes in HbA_{1c}, two observed a rise, and there was no change in five. No change has since been reported by Murray et al.[36] in an open study of 65 adults or in the small 3-month study of Davies et al.[59] Moreover, Abs and colleagues[53] found no change in their database report of 1034 individuals followed for a mean of 0.8 years. Seminara et al.[45] also reported simply that HbA_{1c} remained in the reference range, although scrutiny of the figures in this paper suggests that there may have been a significant rise in mean values. On the other hand, Florakis et al.[51] found that HbA_{1c} rose significantly in 90 individuals followed for 6 months. 24 of these were followed for a total of 24 months and although the authors did not subject the results to statistical analysis, mean ($\pm$ SEM) HbA_{1c} rose in this subgroup from $4.66 \pm 0.08\%$ to $5.19 \pm 0.3\%$. As the authors quote an upper limit to their reference range for HbA_{1c} of 5.1%, it seems likely that this rise was significant, both statistically and clinically. Finally, a rise in mean HbA_{1c} was observed by Christ and colleagues,[42] and a fall was shown to accompany GH withdrawal by Johansson et al.[48]

4.6 Growth Hormone Treatment, Impaired Glucose Tolerance and Diabetes Mellitus

Interpretation of the significance of new cases of IGT and diabetes mellitus during GH therapy is not easy. Either could arise by chance in an individual who is otherwise at risk, and the definition of IGT is made difficult by the known variation that occurs in the glucose response to an oral load. Nevertheless, the occurrence of new cases has been noted by a number of authors. Beshyah and colleagues[38] reported five new cases of IGT during their initial 18-month study of 38 patients (although two were withdrawn at 6 months and the full results reported for only 22); all five cases of glucose intolerance settled when GH was withdrawn. Fernholm et al.[60] reported one case of diabetes mellitus and one case of IGT in their 18-month study of 31 elderly patients with GH deficiency, and Rosenfalck and colleagues[44] noted three cases of IGT in their 30-month open study of 11 patients. Seminara et al.[45] also described three cases of impaired glucose tolerance in 20 children followed for 36 months, but suggested that they were predisposed by reason of an unhealthy diet. Finally, there have been reports of new cases of diabetes mellitus in each of three

large database studies. Blethen et al.[4] described 21 cases of diabetes mellitus in a very large number of children treated with GH, but they did not define the type of diabetes mellitus and it was difficult to be certain from their data if the incidence was greater than expected. Similarly, Abs et al.[53] described six cases of diabetes mellitus in a mean 0.8 years of follow-up of 1034 patients, but because of the selected nature of their population it was not possible to determine if this incidence was excessive. However, the most definitive study was that of Cutfield and colleagues,[5] who observed a 6-fold increase in the incidence of type 2 diabetes mellitus in persons treated with GH during childhood and adolescence, and this figure would be greater if they had used WHO criteria for the definition of glucose intolerance, rather than those of the ADA.[61]

5. Conclusions

5.1 Effect of Growth Hormone on Carbohydrate Metabolism

Despite all the cautions and caveats essential in interpreting the significance of the extensive literature without bias, it is not possible to conclude otherwise than that the balance of evidence indicates that GH has a significant adverse effect on carbohydrate metabolism in clinical practice. The most sensitive indicator of a deterioration in insulin sensitivity is a rise in serum insulin level, whether fasting or after a glucose load, and a clear majority of studies indicate that this typically accompanies the introduction of GH therapy. Rises in blood glucose, whether fasting or after an oral load, would be expected to occur only in those with more marked insulin resistance and/or a defect in insulin secretion and this explains the fact that although increases in glucose have been commonly observed, they are less prevalent than those of insulin. While the development of IGT and diabetes mellitus would be expected in only a small number of those treated, especially in relatively short-term studies, the report by Cutfield and colleagues[5] indicates that the incidence in children and young people may be increased at least 6-fold.

5.2 Some Unresolved Issues

5.2.1 Influence of Baseline Body Mass Index

There is evidence to suggest that some of the conflicts in the literature may be explained by other confounding factors, such as baseline body habitus,[37,57] and this needs further investigation, possibly by retrospective reanalysis of some of the published series.

5.2.2 Partial Compensation

Some authors have noted that effects of GH on carbohydrate metabolism appear to regress with time. Both Christopher et al.[41] and Al-Shoumer et al.[39] noted that although fasting insulin remained elevated during their long-term studies, fasting glucose rose initially, but fell to normal later. Although this has not been a universal experience, and some of it may be explained by population selection, it is possible that some form of compensatory mechanism does indeed occur. Such a mechanism may help explain other paradoxes, such as the discrepancy between the size of the changes in glucose and insulin that have been observed when GH is withdrawn and then reintroduced.[49]

5.2.3 Persistence of Glucose Intolerance after Growth Hormone Withdrawal

One interesting aspect to emerge is that the glucose intolerance and diabetes mellitus which is unmasked, or precipitated, by GH therapy is not always reversible, as would be expected. Thus, persistence of diabetes mellitus after withdrawal of GH was noted by Cutfield and colleagues.[5] Similarly, Chrisoulidou et al.[40] noted an elevation in fasting insulin and AUC for insulin in those who had previously received GH but who had subsequently discontinued it. These observations are inexplicable in the light of current understanding.

5.3 Clinical Significance of Observed Changes on Insulin and Glucose

Many commentators have been inclined to minimise the likely significance of observed changes in insulin sensitivity and glucose intolerance. Some have failed to comment on them in any detail, or have emphasised that any changes that occur are either slight or transient. Nevertheless, the commonly observed increase in insulin resistance is disturbing, given the acknowledged association between insulin resistance and cardiovascular risk. Similarly, rises in plasma glucose and HbA_{1c} which have been reported, even within the normal range, could well be associated with a significant increase in cardiovascular mortality.[12] However, it must not be forgotten that other changes accompany the introduction of GH treatment, and these include a reduction in fat mass and central adiposity, a probable reduction in the circulating concentration of total and low-density lipoprotein cholesterol (although other changes in lipid profile, both beneficial and not, are more variable), and changes in vascular structure which are possibly indicative of reduced atherogenesis. Hence, it is not currently possible to predict the net effect of GH on cardiovascular risk, but there is a possibility that it may make it worse. There remains an overwhelming need for further large, long-term, randomised, observer-blind studies to evaluate both the efficacy and safety of GH therapy before it is adopted in routine practice. It is to be hoped that such a study would help identify those who might benefit from GH replacement therapy, as well as those who might be put at increased risk.

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