Glucose homeostasis in acromegaly: pathogenesis and effects of treatment

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Summary

Acromegaly is a chronic debilitating disorder resulting from excessive secretion of growth hormone (GH) and consequent increase in insulin-like growth factor I (IGF-I), usually caused by a pituitary somatotroph adenoma. Effective treatment aims to ameliorate symptoms and signs of the disease and to lower mortality rate. In particular, high morbidity and mortality are partly related to the presence of insulin resistance due to the action of GH on liver, muscle and adipose tissue. Insulin resistance and/or reduced insulin sensitivity physiologically result in hypersecretion of insulin from the pancreas. This compensatory state of hyperinsulinemia is felt to be a first and more important marker for this condition. Adequate control of GH excess by surgery or pharmacotherapy is associated with decreased insulin resistance, resulting in reduced plasma insulin and glucose levels or improved glucose tolerance. Despite divergent effects of both somatostatin and somatostatin analogs on GH, insulin and glucagon secretion, and glucose absorption, treatment with the somatostatin analogs octreotide and lanreotide has only limited effects on glucose metabolism. However, glucose sensitivity has been formally examined using a hyperinsulinemic euglycemic clamp only in a minority of studies. Treatment with the GH-receptor antagonist pegvisomant improves insulin sensitivity, thus decreasing circulating fasting insulin and glucose levels. Assessment of insulin secretion and glucose levels in acromegalic patients during administration of the above compounds is thus mandatory.

KEY WORDS: acromegaly, insulin-resistance, glucose homeostasis, pegvisomant, somatostatin analog, octreotide, lanreotide.

Introduction

Acromegaly is a rare but severe endocrine disease resulting from the increased release of growth hormone (GH) and, consequentially, insulin-like growth factor I (IGF-I) usually induced by a pituitary adenoma. This slowly developing syndrome occurs with the same frequency in men and women at any age and is characterized by an increased mortality because of cardiovascular, respiratory, metabolic and oncologic complications (1, 2).

The therapeutic goal in acromegaly is to reduce morbidity and mortality by removing tumor mass and restoring GH and IGF-I values to normal range for age and sex. High morbidity and mortality are reported associated to insulin resistance due to the action of GH on liver, muscle and adipose tissue (3-5).

Current available treatments for acromegaly include neurosurgery, radiotherapy and medical therapy with dopamine-agonists, somatostatin analogues and the GH-receptor antagonist. In experienced hands, surgery is able to induce the definitive cure from acromegaly, according to the international criteria of cure (6), in approximately 60% of patients (7). However, in patients with large invasive tumors, representing the vast majority of cases, surgery fails to achieve the complete tumor removal and surgical effectiveness is lower (8).

Radiotherapy, both conventional external-beam or stereotactic radiosurgery with the use of gamma-knife, is indicated for patients with recurrence or persistence of disease activity after unsuccessful surgery and resistant or intolerant to medical treatment. However, limitations of radiotherapy include the very slow attenuation of GH and IGF-I levels, requiring more than 10 years to achieve the maximum hormonal control (9),

and sometimes the secondary damage of near cerebral tissue or hypopituitarism (10, 11).

Dopamine-agonists, such as bromocriptine and cabergoline, are only partly effective (12). Particularly, a recent meta-analysis (13) showed that cabergoline is effective in inducing IGF-I normalization in 52% of patients with mild hormonal excess, with a poor effectiveness in those with aggressive disease. Somatostatin agonists inhibit the secretion of growth hormone, but GH and IGF-I normalization is achieved in approximately 70% of patients (14).

Acromegaly is also associated with alterations of lipid metabolism, with the incidence of hypertriglyceridemia being three times higher than normal population (15). The reduction of GH to "safe" levels (< 2.5 µg/L) has been reported to reduce mortality rate (16, 17); therefore, the aim of all treatments is to induce disease control by suppressing GH/IGF-I hypersecretion to normal levels and to prevent complications.

This review aims at focusing on insulin resistance, a known cause of metabolic complications commonly associated to acromegaly, and particularly on its pathogenesis and the role of the different therapeutic approaches.

Epidemiology

It is known that growth hormone counteracts insulin action on peripheral tissues causing insulin resistance (18). Some studies have reported on a direct correlation between circulating GH plasma levels and the degree of glucose intolerance (19). Noteworthy, the development of glucose intolerance has been related to family history of diabetes and to the presence of hypertension (20). Although limited data are available regarding the role of insulin action in acromegalic patients, the observation of hyperinsulinemia and/or impaired glucose tolerance in acromegaly suggests that chronic hypersecretion of GH is associated with insulin resistance (4, 21-27). The prevalence of overt diabetes mellitus in acromegaly largely differs among studies, likely due to different patient series and ethnicity, higher age and longer disease duration, family history of diabetes, concomitant presence of arterial hypertension and hormonal levels. The prevalence of impaired glucose tolerance ranged from 16 to 46% among studies (28-30), whereas diabetes mellitus occurs in about 10-25% of acromegalic patients and it has been associated with increased mortality (2). Furthermore, in acromegaly dyslipidemia is frequently reported; particularly hypertriglyceridemia occurs in 19 to 44% of patients and a positive correlation between the serum insulin response to glucose load and increased serum triglycerides concentrations has been described (15). The increased cardiovascular morbidity and mortality are, at least partly, consequent upon the presence of insulin resistance and dyslipidemia.

Moreover, in hyperinsulinemic patients blood pressure is reportedly increased, and hyperinsulinemia-induced sodium reabsorption may contribute to the increase in blood pressure in acromegalic patients (31). In an open transversal study, 130 consecutive treatment-naive acromegalic patients were evaluated for glucose metabolism and blood pressure (20), showing glucose tolerance abnormalities and hypertension respectively in 54% and 35.4% of cases. Particularly normotensive patients with glucose tolerance alterations had an increased prevalence of impaired diastolic (40%) and systolic (32%) dysfunction (20).

Pathogenesis

Insulin resistance and/or reduced insulin sensitivity physiologically result in the pancreatic hypersecretion of insulin. This compensatory state of hyperinsulinemia is felt to be a first and more important marker for this condition. Insulin resistance is characterized by a reduced response to a given amount of insulin (32) and occurs in several diseases, including diabetes mellitus (32, 33). It has been demonstrated that after oral glucose tolerance test (OGTT) acromegalic patients with either normal or impaired glucose tolerance have reduced peripheral tissue glucose uptake, likely due to the insulin resistance in extra-hepatic tissue (3, 34, 35). The underlying pathophysiological mechanisms are yet to be clarified, but a possible direct action of GH excess at receptor level has been proposed. GH hypersecretion appears to be associated with downregulation of insulin receptors (IR), and decreased IR binding affinity has been found in liver and skeletal muscle of transgenic mice for GH (36-38). In acromegalic patients, changes in IR binding affinity, as well as a decreased receptor expression and an increase in the affinity of the unoccupied or empty receptor are reported (35). These changes have been correlated to each other, as well as to the severity of the increase in plasma insulin and GH levels. In experimental conditions of prolonged exposure to chronic GH excess, changes in IR auto-phosphorilation or kinase activity have been found in rats (39-41). On the other hand, a post-binding alteration in insulin action in hepatic and extra hepatic tissues has also been proposed (4, 35). The decrease in maximally stimulated glucose utilization and the lack of change in monocyte and erythrocyte insulin binding suggest an impairment in post-binding function (4). Several post-receptor events are affected when cultured cells are exposed to GH, suggesting that GH and insulin signalling may converge at post-receptorial levels (42-44). GH has also been shown to promote tyrosine phosphorylation of IRS-1 and IRS-2 and their association with PI-3 kinase in different GH responsive tissues (45-48). Another mechanism by which GH exerts insulin resistance is by the induction of some cellular proteins, such as SOCS-1 and SOCS-6, that are able to inhibit IR signalling (49). A role of pancreatic β-cell dysfunction in the pathogenesis of glucose intolerance in acromegaly was also postulated: by comparing plasma pro-insulin, immunoreactive insulin, C-peptide and blood glucose concentrations during oral glucose load in normotolerant acromegalic patients, it has been shown that acromegalics had higher fasting insulin, pro-insulin and C-peptide levels than controls, thus suggesting ei-

ther that hyperproinsulinemia contributes to hyperinsulinemia, and that prolonged and excessive GH secretion may affect pancreatic beta-cell function (35). In acromegaly, glucose metabolism abnormalities progressively occur: in the early stage patients show hyperinsulinism with normal or borderline glucose tolerance. In the middle phase, a delayed insulin peak after glucose load associated to normal or slightly impaired glucose tolerance is reported. The third and last stage is characterized by maximal pancreatic response in fasting conditions with no further rise in insulin concentrations after glucose injection (35).

The incidence of hypercholesterolemia is similar to that of the general population, and different independent studies reported plasma cholesterol to be increased (50), normal (51) or decreased (15) in patients with acromegaly. Furthermore, an increased plasma concentration of lipoprotein (a), small dense LDL and remnant-like lipoprotein particles (RLP) has been reported (51-53). The incidence of type IV hypertriglyceridemia is three times higher than in normal population (15). Lecithin/cholesterol acyl transferase (LCAT), phospholipids transfer protein (PLTP) and cholesteryl ester transfer protein (CETP) are proteins involved in the intravascular metabolism of lipoprotein. Plasma CETP, LCAT and PLTP activity has been found decreased in acromegalic patients (54), possibly contributing to increased cardiovascular risk in these patients due to impaired reverse cholesterol transport.

In summary, in acromegaly it is not possible to identify a unique sequence of events leading to insulin resistance. The primary defect is clearly the high levels of GH; secondly, the plasma GH levels could directly act in increasing basal insulin concentrations which in turn could cause the decrease in receptor concentration and the alteration in the post-receptorial mechanisms.

Effects of GH/IGF-I Suppression on insulin resistance

Biochemical control of acromegaly by normalization of either GH or IGF-I levels predicts improvement in glucose homeostasis (55). Both surgery and medical treatment resulting in biochemical cure of acromegaly have been shown to normalize fasting glucose and insulin values (55).

Surgery
Glucose tolerance abnormalities dramatically improves when normalization of circulating GH levels is achieved by successful surgical or pharmacological therapy. Impaired glucose tolerance (IGT) and diabetes mellitus are potentially cured if surgical tumor resection is complete and plasma GH levels are normalized, which occurs in approximately 70% of acromegalic patients, whereas in 30% of cases impaired glucose tolerance could persist (56). Increased insulin secretion may still occur after glucose adminis-

tration in some patients despite the normal glucose metabolism and fasting insulin levels (57).

Radiotherapy
A few studies have investigated the effects of radiation therapy on glucose metabolism in acromegaly and limited data are nowadays available. However, radiotherapy treatment has reportedly positive effects on glucose metabolism: the reduction in plasma GH levels after radiotherapy correlate with the improvement of glucose tolerance (58).

Pharmacological therapy
Somatostatin analogs (SA) significantly improve GH/IGF-I control, in particular in those patients not completely cured by surgery (59). The effectiveness of medical therapy either with SA or dopamine agonists in improving glucose metabolism is controversial. Octreotide is a SA which has been shown to be effective in the treatment of acromegaly. It has been reported that octreotide has beneficial effects on carbohydrate metabolism. Ho et al. evaluated the effects of this SA by performing a glucose tolerance test and an euglycemic hyperinsulinemic clamp (60) showing the normalization of glucose tolerance in 4 out of 5 patients with impaired glucose tolerance without a significant change in mean insulin concentrations. Thus the authors conclude that octreotide improves both glucose metabolism and insulin sensitivity by an increased ability of insulin to suppress hepatic glucose production; however the peripheral glucose uptake was not affected by treatment. A positive experience has been reported by Colao et al. (61). They reported the normalization of blood glucose levels in 3 out of 7 acromegalic patients affected by diabetes and in 2 patients insulin has been replaced by oral hypoglycemic agents, and in other 2 patients insulin dosage was reduced. The improvement in glucose metabolism was associated with a significant reduction in serum GH and IGF-I levels. However octreotide is not always capable to ameliorating carbohydrate metabolism; there are some reports showing that it deteriorates glucose tolerance in patients with acromegaly. The International Multicenter Acromegaly Study Group (62) evaluated the clinical and biochemical effects of long-term therapy with octreotide and reported a worsening of glucose tolerance in 48% of 25 assessed patients. In 2 out of 25 acromegalic patients there was an ameliorating carbohydrate metabolism. Another study (63) investigated the effects of the SA on glucose tolerance in 90 acromegalic patients. At baseline 11 patients were diabetic, 24 had an impaired glucose tolerance and 55 had normal glucose tolerance. During octreotide therapy about 20% of patients who had normal carbohydrate metabolism have developed impaired glucose tolerance and 29% became frankly diabetic; 3 of 11 patients who were diabetic at baseline became normal (18%) or developed impaired glucose tolerance (9%). No relationship was observed between the dose of octreotide and the change in glu-

cose tolerance. Patients with elevated baseline insulin levels were more likely to become diabetic; so this study has showed a significant deterioration in glucose metabolism both in acromegalic patients with normal and impaired glucose tolerance. In the Italian Multicenter Octreotide Study (64) it has been shown that SA treatment is able to deteriorate the glucose tolerance in acromegaly: 25% of patients with overt diabetes mellitus had an impairment of their metabolic control after treatment with octreotide. The divergent effects of octreotide on glucose tolerance may be explained by the multiple complex effects of this drug on glucose metabolism (65, 66). Octreotide may induce an increase in blood glucose concentration by inhibiting insulin secretion from pancreatic beta cells. Moreover it has been reported that this SA increases IGF-BP-1 concentration counteracting the insulin-like effect of IGF-I (67, 68). On the other hand octreotide may induce a decrease in blood glucose levels by inhibiting GH and IGF-I hypersecretion. The reduction in circulating GH levels can induce an inhibition of gluconeogenesis and an increase of insulin sensitivity with an improved insulin action both at the receptor and post-receptor level. Furthermore octreotide inhibits the secretion of insulin, glucagon and other intestinal hormones, reduces gastrointestinal movements and consequently glucose absorption. These multiple effects of octreotide at different steps involved in glucose metabolism may explain the individual differences and the unpredictable effect of this drug on glucose tolerance in acromegalic patients also if the genetic background of these patients must be taken in consideration. The long-term follow up studies with long-acting SA do not show any impairment of glucose tolerance (69-71). Further studies are necessary to elucidate the effects of these new formulations on glucose tolerance. We have published a paper where twenty-four active acromegalic patients were studied in order to determine the long-term effects of octreotide-LAR and SR-lanreotide on insulin sensitivity and carbohydrate metabolism (27). All patients underwent an oral glucose tolerance test (OGTT) and 12 also had an euglycaemic hyperinsulinaemic clamp and were evaluated at baseline and after 6 months of SA therapy. The results of these paper showed that acromegalic patients had low M-values (insulin sensitivity index) in respect to the control group at baseline, followed by a significant improvement after 6 months of therapy. Moreover serum glucose levels at 120 min during OGTT worsened during SA therapy in patients with normal glucose tolerance, but not in those with impaired glucose tolerance or diabetes mellitus. This was associated with a reduced and 30 min delayed insulin secretion during OGTT. Also, HbA1c significantly deteriorated in all subjects after treatment. It was concluded that in acromegalic patients SA treatment reduces insulin resistance, and also impairs insulin secretion suggesting the use of oral secretagogue hypoglycaemic agents and/or insulin therapy as treatment of choice in acromegalic patients who develop frank hyperglycaemia during somatostatin analogs therapy. More recent evidences reported a similar prevalence of deterioration and improvement of glucose tolerance 12 months after first-line SA treatment (72, 73), with uncontrolled acromegaly despite SA therapy and abnormal glucose tolerance at baseline being associated with glucose tolerance worsening. A recent study by Giordano C et al. (74) compared the effects of first-line SA or surgery on glucose metabolism in acromegaly. Both treatments have been shown to improve insulin sensitivity and visceral adiposity index (VAI), a new marker of metabolic syndrome. Interestingly, successful treatments able to normalize disease activity and to ameliorate glucose tolerance have been shown to shortly result in the improvement of quality of life in acromegalic patients (74, 75).

Dopamine agonists have controversial effects on glucose tolerance, and no significant effect on glucose metabolism has been reported (76).

New perspectives derive from pegvisomant, a pegylated GH analog that competes with wild-type GH for GH receptor binding sites and prevents functional GH receptor dimerization, by the inhibition of the signal transduction and IGF-I generation (77).

Pegvisomant-induced normalization of serum IGF-I, an accepted marker of GH-dependent disease activity (77), has been reported in approximately 80% of acromegalic patients proven to be resistant to long-term conventional SA therapy (78, 79). Control of acromegaly induced by pegvisomant has been associated with an improvement of glycometabolic profile: several studies (80-85) have demonstrated that pegvisomant induces a significant decrease in fasting glucose until normal levels also in patients with diagnosed diabetes mellitus and impaired glucose tolerance, and improves insulin resistance by the reduction of HOMA-index and the increase of pancreatic β-cell secretory function (HOMA-β).

Co-administration of pegvisomant and SA showed discordant effects on glucose homeostasis in different series of acromegalic patients (86-88). However, it is a matter of fact that a good control of hyperglycemia can be successfully achieved in the majority of acromegalic patients with overt diabetes or impaired glucose tolerance, independently on the administered treatment to control GH excess.

Only a study (89) compared the effects of SA and pegvisomant, either as monotherapy or combined treatment, on glucose profile in acromegaly. Fasting plasma glucose levels significantly vary during the study, being highest during SA treatment and lowest levels during pegvisomant therapy: 5.9 ± 0.3 mmol/L while on somatostatin analogs, 5.4 ± 0.4 mmol/L in active patients after somatostatin analogs discontinuation, 5.0 ± 0.2 mmol/L during pegvisomant 10 mg , 4.7 ± 0.2 on pegvisomant 15 mg, and 5.3 ± 0.3 while on combined treatment (p= 0.02).

When both surgical or medical treatment of acromegaly are ineffective in ameliorate the glucose intolerance and insulin resistance it should be necessary to start a specific treatment.

In conclusion, glucose homeostasis disorders occur in at least one third of acromegalic patients. GH and IGF-I excess lead to insulin resistance by increasing

basal insulin concentrations and/or affecting receptor expression and post-receptorial mechanisms. Disease control is associated with a significant improvement of insulin resistance and glycometabolic profile, although medical therapy with SA is reported to induce either deterioration or improvement of glucose tolerance, with uncontrolled acromegaly despite SA therapy and abnormal glucose tolerance at baseline being associated with glucose tolerance worsening. Pegvisomant improves insulin resistance and induces a significant decrease in fasting glucose up to normalization in acromegalic patients with diagnosed diabetes mellitus and impaired glucose tolerance. Further studies are still needed to confirm and extend these data.

Acknowledgements

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