

Extra-hepatic Acromegaly

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Abstract

After the introduction of somatostatin analogs (LA-SMSA) and the growth hormone (GH) receptor antagonist, pegvisomant (Peg-v) normal serum insulin-like growth factor-1 (IGF-1) concentrations in virtually every patients with acromegaly is possible. The impact of these products on the GH-IGF1 axis is completely different. We advocate that LA-SMSA may normalize serum IGF1 levels in the presence of elevated GH actions in extra-hepatic tissues. This results in persistent peripheral disease activity that we call 'extra-hepatic acromegaly'. Peg-v competitively blocks systemic GH action and results in a GH serum level increase. Therefore high doses of Peg-v are necessary to control IGF-1. Since the mode of action differs between these products, it is questionable if identical IGF-1 levels, during Peg-v or LA-SMSA are really identical representations of the biochemical situation. With the traditional biomarkers medical treatment is therefore difficult to monitor with the traditional biomarkers. Additionally, Peg-v and LA-SMSA could be ideal combination since they have different mode of actions. We believe that the time has come to challenge the existing concepts of treatment and monitoring of patients with acromegaly.

Keywords

Acromegaly, extra-hepatic acromegaly, somatostatin analogs, growth hormone receptor antagonist, Pegvisomant, growth hormone sensitivity, growth hormone deficiency, IGF-1

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Acromegaly is a rare disease and in majority of cases caused by a growth hormone (GH)-producing pituitary adenoma. More than 75 % of these adenomas are macroadenomas.¹ Acromegaly is characterized by excessive skeletal growth, soft tissue enlargement and reduced quality of life. The cornerstone of the diagnosis acromegaly consists of insufficient GH suppression during oral glucose loading and elevated insulin-like growth factor-1 (IGF-1). Treatment is aimed at a reduction of sign and symptoms, improved quality of life, and a decrease in morbidity and mortality.² Depending on patients' characteristics, pituitary adenoma size, and localization, a treatment modality should be chosen. Available modalities are surgery, medical therapy, radiotherapy, or a combination of these. To date, treatment modalities mainly focus on the normalization of IGF-1 serum levels.

The obvious advantages of IGF-1 is that the efficacy of different modalities can easily be compared by unsimilar senses of IGF-1, since this is more practical than frequent GH measurement. However this would imply that identical IGF-1 levels from different treatment modalities represent an identical metabolic situation. It can be argued that this assumption is invalid. For instance a similar IGF-1 serum level during somatostatin analogs (LA-SMSA) or receptor antagonists (GHR), pegvisomant (Peg-v), may be biochemically completely different for a patient.

LA-SMSA reduces the production of GH directly via their action on the pituitary tumor. Peg-v suppresses the actions of GH systemically in its target tissues as e.g. the liver and peripheral tissues. So, the modes of

action of these two products are completely different. IGF-1 levels are under direct control of GH, but portal insulin concentrations are also an important factor. LA-SMSA reduce the levels of portal insulin by their suppressive action on beta cells in the pancreatic islets.^{3,4} Additionally, LA-SMSA also decrease IGF-1 production in the rodent liver GH independently.⁵ These factors might result in an underestimation of disease activity as IGF-1 levels during LA-SMSA are already reduced by the GH independently effect of LA-SMSAs on IGF-1 concentration. When IGF-1 levels are within the normal range, clinicians might conclude that this is the result of direct GH suppressive effect of the LA-SMSA and thereby ignoring the GH independent effects on the liver IGF-1 production. However, other nonhepatic tissues, all with their own sensitivity to GH, like kidney, bone, and adipose tissues might still experience a relatively high GH action resulting in signs and symptoms. In this article we will describe these effects as the concept of 'extra-hepatic acromegaly'.⁶

Similarities and Differences Between Actions of GH and IGF-1

To further address extra-hepatic and hepatic acromegaly, a better understanding of the GH-IGF-1 axis in different metabolic situations is necessary. It is hard to address the individual effect of GH and IGF1 in psychologic conditions at a tissue level.

The liver is the main producer of serum IGF-1 and this production is GH dependent. IGF-1 and GH are both strong growth promoters. However, GH possesses anti-insulin or diabetogenic activity.⁷ GH reduces the storage

of glycogen in the liver and promotes gluconeogenesis and lipolysis. On the other hand, insulin and IGF-1 have similar actions, this clearly demonstrates that GH and IGF-1 exhibit different physiologic actions.

This was nicely addressed in several mouse studies. List et al. treated diet-induced obese type 2 diabetic mice with four different doses of GH.⁸ Body composition and weight, insulin, IGF-1 levels, fasting glucose, liver triacylglycerol, tissue weight, glucose tolerance, and blood chemistry were assessed. A GH dose-dependent increase in lean mass and decrease in fat mass were observed. These body composition changes are observed in the two highest GH dose groups, however, only the highest GH dose resulted in an elevated serum IGF-1 concentration.⁸ Additionally, lean body mass increased before the decrease of subcutaneous and mesenteric white adipose tissue (WAT). This demonstrates that GH actions and IGF-1 do not occur at the same time points. These observations are in agreement with previously published studies in which subcutaneous WAT depots increased in mice that lack GH actions.⁹⁻¹¹ Another example of a GH independent effect was described in a study with liver-IGF-I deficient (LID) mice in which growth and development did not differ between control and LID mice.¹²

Another rodent study showed that mice with high GH and IGF-1 levels develop more rapidly progressive glomerulosclerosis than mice with only high IGF-1 levels.³ These high IGF-1 mice only, developed glomerulosclerosis in a much slower way, as a result of an inactivated GH gene.^{13,14} Both studies concluded, that GH is able to influence the kidneys independently. A consecutive study confirms these results with transgenic mice producing bovine GH-analogs (with following changes; L121P and E126G). These animals have normal IGF-1 levels and normal size, but developed glomerulosclerosis just as severe as mice that express wild-type bovine GH.¹⁵

Supplementary studies, performed with mice that express a GH antagonist, observed that these mice were protected against streptozotocin-induced glomerulosclerosis.^{16,17} Glomerulosclerosis could be prevented in these two studies on the transgene (GH antagonist) mice and in mice that were injected with a GHR antagonist (G120K-PEG) even without reduction of the IGF-1 levels.¹⁸

These mice studies show that GH can have tissue specific effects independent of elevations of IGF-1 serum levels. The effects of GH on peripheral tissues differ per tissue. Especially sensitivity for GH of the liver greatly depends on the metabolic situation.

The Important Impact of (Portal) Insulin on Hepatic Growth Hormone Sensitivity

During prolonged fasting, carbohydrates rapidly exhaust and alternative energy can be utilized from the lipid stores. Since IGF-1 has insulin like effects, it makes teleologic sense that hepatic IGF-1 decreases during prolonged fasting in mammals. Leung et al. observed that GH-induced hepatic IGF1 output is regulated by insulin concentration in the portal vein.⁵ Insulin was able to stimulate the translocation of GHR to the surface of the hepatocyte.⁵ Low insulin concentration in the portal circulation reduced GHR expression on the hepatocyte surface and result in a GH 'resistant' liver. While high portal insulin concentration increase liver GHR expression and increase GH sensitivity of the liver for GH and

ultimate increase IGF-1 output from the liver.⁵ Simultaneously, portal insulin suppresses the production of IGFBP1 (IGF-1 Binding Protein) by the liver, which could increase bioavailable IGF-1.^{19,20}

There is a human state of low levels of portal insulin, type I diabetes mellitus (DM1). Restoring the portal insulin concentration in DM1 has an impact on IGF-1 serum concentration.²¹ Only when insulin was replaced in the portal vein, IGF-1 level increased into the normal range and a decrease in GH levels.²¹ When insulin was replaced subcutaneous, by continuous or intermitted administration, IGF-1 concentrations were low and GH levels were elevated.²¹ Others reported on the effects of GH administration in DM1 patients with and without residual β -cell function, assessed by C-peptide.²² GH induced an increase in IGF-1 serum concentration only in the C-peptide positive group, DM1 with residual β -cell function.²²

Acromegaly patients treated with LA-SMSA have similarities with these DM1 patients: both display high systemic GH activity combined with a relative GH resistant liver due to low levels of portal insulin. While Peg-v treated acromegaly patients have similarity with DM2 patients; both display low systemic GH activity combined with a relative GH-sensitive liver due to high or normal levels of portal insulin. We previously called this metabolic situation 'extra-hepatic acromegaly'.

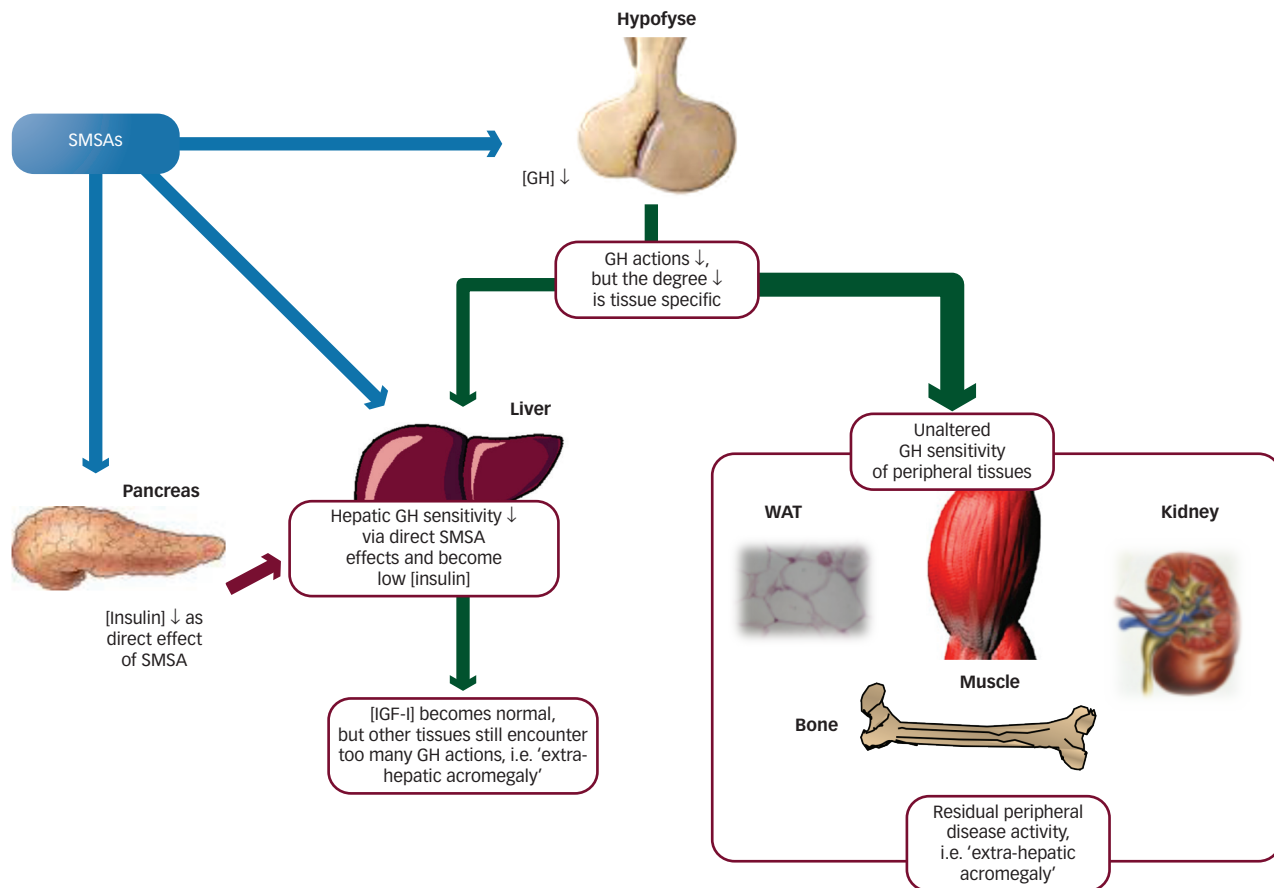
The Effect of LA-SMSA

Somatotroph adenoma cells express different subtypes of somatostatin receptors of which subtypes 2 (sst2) and 5 (sst5) have the highest expression in the adenoma.²³ The therapeutic effect of LA-SMSA is mainly mediated by the sst2 and sst5 receptors, although with different affinities.²⁴⁻²⁶ Somatostatin analogs decrease the pathologic GH secretion that is translated in a reduced hepatic IGF-1 production.^{24,27} Sst2 and sst5 are not only expressed in somatotroph cells but among others in pancreatic islet cells.^{3,4} Glucagon and insulin levels will both decrease in the presence of LA-SMSA^{3,4} which can result in a worsening of the glycemic control in acromegaly patients. This LA-SMSA mediated decrease in portal insulin results in hepatic GH resistance, which results in a suppression of hepatic IGF-1 production.⁵ The hepatic GH resistance will result in a decrease in serum IGF-1 levels, which does not necessarily reflect the peripheral GH activity on other tissues (see *Figure 1*).

In two humans studies GH independent IGF-1 decrease has been observed after the administration of somatostatin analogs.^{28,29} Both studies administered octreotide for 7 consecutive days during GH treatment in adult GH deficient (GHD) patients. The administration of octreotide resulted in a 16-18 % decrease of IGF-1 serum levels and an increase in IGFBP1 levels and a decrease in insulin levels.^{28,29}

These data would suggest that a normal IGF-1 in acromegaly patients, during LA-SMSA does not necessarily imply a control of GH action in the peripheral tissues (see *Figure 1*). This is the condition that we would call 'extra-hepatic acromegaly'. A recent study further addressed the effects of LA-SMSA in acromegaly patients by comparing health status, and biomarkers in patients that were controlled after surgery or by LA-SMSA treatment. Both groups had similar and normalized IGF-1 levels, but the LA-SMSA group had less suppressed GH levels and less symptom relief.³⁰ The authors suggest that LA-SMSA treatment specifically suppresses hepatic IGF-1 production and too lesser extend GH levels. Similarly, others

Figure 1: Effects of Somatostatin Analogs (SMSAs) in SMSA-sensitive Acromegalic Subjects



Red arrows indicate inhibitory effects; green arrows indicate stimulatory effects, while thickness of arrow indicates level of inhibition. GH = growth hormone; IGF-I = insulin-like growth factor-I; SMSAs = somatostatin analogs; WAT = white adipose tissue.

have found similar results that normal levels of IGF-1 are poor predictors of quality of life (QoL) in acromegaly patients treated with LA-SMSA.^{2,31,32}

The Effect of Pegvisomant on Peripheral Tissues

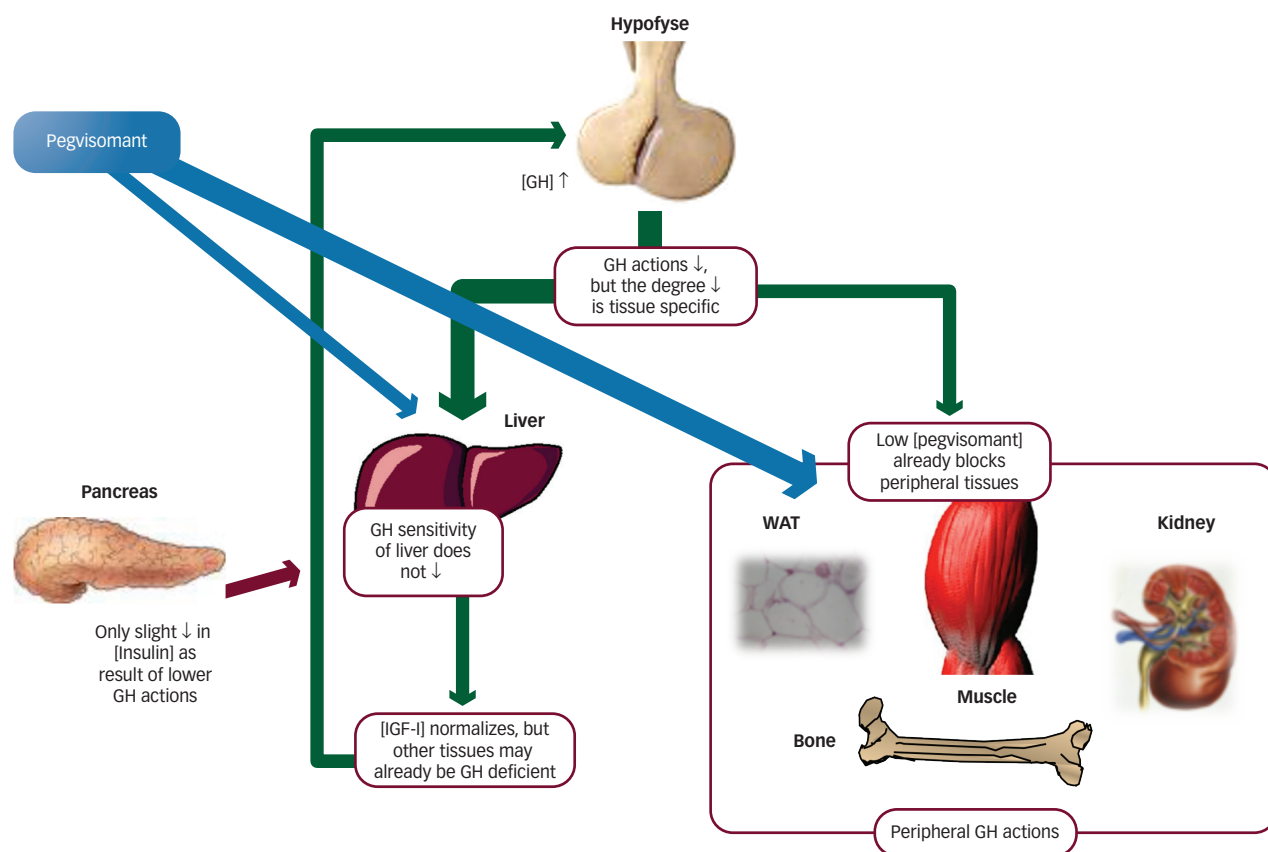
Peg-v is a competitive GHR-antagonist.³³⁻³⁵ The higher the GH level, the higher the dose of Peg-v needed to block the effects of the endogenous GH molecules.³⁶ The peripheral tissues as WAT, the kidney and the skeletal muscle need less Peg-v to reduce GH actions compared to those quantities of Peg-v that are needed to normalize hepatic IGF-1 production (see Figure 2).¹⁸ A Danish study supports this, they reported that Peg-v could suppress lipolysis in healthy subjects at low dosages without any change in circulating and local IGF-1 levels.³⁷

So, in a dose dependent manner Peg-v seems to suppress peripheral GH actions prior to the normalization of hepatic IGF-1 production. This condition that is the result of Peg-v treatment could be called 'hepatic acromegaly'.

A Balance of Two Opposing Features

To date, somatostatin is the drug of choice in acromegaly patients with insufficient suppression of IGF-1 after surgery or when surgery is not feasible.³⁸ If LA-SMSA alone do not normalize IGF-1, a switch to Peg-v treatment, as mono-therapy or in combination with LA-SMSA should be

considered.^{39,40} So, to date combination treatment of Peg-v and LA-SMSA is mainly focused on patients with an insufficient biochemical response to LA-SMSA, but we believe that many other patients could benefit. The strongest evidence for this was observed in a study where Peg-v was added to so-called controlled patients during LA-SMSA treatment.³² The hypothesis was that an improvement in QoL and metabolic parameters could be observed after the introduction of Peg-v, without any change in their current LA-SMSA treatment. In this prospective, a double blind, placebo-controlled, crossover study with 20 patients with normal IGF-1 levels during LA-SMSA, QoL was assessed by acromegaly QoL questionnaire (AcroQoL)⁴¹⁻⁴³ and signs and symptoms by the patient-assessed acromegaly symptom questionnaire (PASQ).³⁶ Two consecutive periods of 16 weeks with Peg-v and placebo, were divided by a wash out of 4 weeks. The primary efficacy parameter was improvement in QoL assessed by the AcroQoL. During the Peg-v co-treatment period the QoL and signs and symptoms improved significantly compared with baseline, without any change in serum IGF-1 levels. Not all dimensions or questions of the AcroQoL or PASQ changed significantly. In the AcroQoL mainly the total score and the physical dimension changed, and in PASQ patients reported less perspiration, soft tissue swelling, and a better overall health status. It may be true that IGF-1 could have changed if the group of patients was larger or if IGF-1 was assessed within 2 days after Peg-v administration. The patients that changed in AcroQoL also lost bodyweight and regained it after Peg-v was discontinued for 2 weeks. These quick changes in weight

Figure 2: Effects of Pegvisomant in Acromegalic Subjects

Red arrows indicate inhibitory effects; green arrows indicate stimulatory effects, while thickness of arrow indicates level of inhibition. GH = growth hormone; IGF-I = insulin-like growth factor-I; WAT = white adipose tissue. Adapted from Neggers S. et al., Eur J Endocrinol, 2011;164:11–6.

may be explained by fluid retention or loss, which is a typical effect that can be observed during GH treatment. Furthermore, the higher levels of energy i.e. lower level of fatigue, and the change in the soft tissue swelling and perspiration are typical changes that one can see during GH substitution in a GH deficient patient. In acromegaly patients with elevated IGF-1 levels the same symptoms in the PASQ scores, perspiration and soft tissue swelling, also decrease after PEG-V treatment. This seems to occur without a significant correlation with change in IGF1 levels.⁴⁴ This all could support the concept of extra-hepatic acromegaly.

A recent study of the Danish group that assessed QoL, by no disease-specific questionnaires, in controlled patients during LA-SMSA did not observe any changes in QoL after the addition of Peg-v.⁴⁵ However the design of the study, the use of a disease nonspecific questionnaire and change in LA-SMSA dose after the introduction of Peg-v may be an explanation for the different findings.

Future Developments

To date, with the availability of Peg-v, biochemical control of acromegaly is possible in almost all patients. Thus, it might be an appropriate moment for a re-evaluation of treatment options. We would like to postulate that IGF-1 is not always a reliable biomarker for disease activity.² LA-SMSA decrease pituitary GH production but they have important additional effects, namely decreased portal insulin levels and hepatic IGF1

production that may lead to a normal IGF1 serum level but with residual disease activity in the peripheral tissue, which we call extra-hepatic acromegaly. For sure, more studies are needed to confirm and further characterize extra-hepatic acromegaly, and what the optimal treatment will be. If simply increasing LA-SMSA dose will do, or the addition of Peg-v is better to treat this residual peripheral GH activity.

Peg-v as treatment is challenging since it will result in an increase in GH levels³⁶ and may decrease peripheral GH action prior to the GH action in the liver. The complementary actions of Peg-v and LA-SMSA make the combination an attractive option. There is evidence for superiority to LA-SMSA monotherapy in terms of disease-specific QoL, glucose homeostasis.⁴⁶ But this does not solve the problem of suboptimal marker of disease control IGF-1. Therefore, there is a need for a reliable bioassay that can assesses disease-specific activity. To date, no reliable sign/symptom (score)/biochemical marker that reflects disease activity has been identified. A novel biochemical parameter that would be able to assess tissue-specific disease activity is a necessity.

We hope that our concept of extra-hepatic acromegaly will challenge the medical and pharmaceutical community to design and conduct studies to prove that we are wrong or right and look for more specific biomarkers of disease activity that will optimize treatment for the individual patient with acromegaly. ■

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