CLINICAL STUDY

Pegvisomant increases intra-abdominal fat in patients with acromegaly: a pilot study

U Plöckinger and T Reuter

*Interdisziplinäres Stoffwechsel-Centrum: Endokrinologie, Diabetes und Stoffwechsel, Med. Klinik m S Hepatologie und Gastroenterologie, Charité-Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany**(Correspondence should be addressed to U Plöckinger; Email: ursula.ploekinger@charite.de)*

Abstract

Objective: Acromegalic patients have increased lipolysis and decreased fat mass as well as reduced insulin sensitivity and glucose intolerance. During somatostatin analog therapy, these changes persist despite GH suppression, but they are now due to drug-induced suppression of insulin secretion. By contrast, during pegvisomant (PEG) therapy, GH no longer stimulates lipolysis due to the blockade of its receptor, while insulin action is unabated. Hence, both insulin sensitivity and fat mass, including intra-abdominal fat, should increase. We therefore studied intra-abdominal fat and insulin resistance in acromegalic patients after a 3-month octreotide-washout period, i.e., during untreated acromegaly, and during PEG treatment.

Methods: Five acromegalic patients, not controlled on octreotide (OCT) therapy, were studied after 3-month OCT washout and 6-month PEG therapy. Insulin sensitivity was determined by homeostatic model assessment value and hyperinsulinemic, normoglycemic clamp. Subcutaneous and intra-abdominal fat were measured by electron beam computed tomography.

Results: During PEG therapy, all the patients had normal, age-adjusted IGF-I concentrations. Compared with washout, insulin sensitivity (HOMA and *M* value) was not significantly different. However, intra-abdominal fat mass increased significantly during therapy (median (range) cm²: 112 (84–480) and 172 (112–524) respectively, *P* < 0.05), while subcutaneous fat was not significantly different. Low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides remained unchanged.

Conclusions: During PEG therapy of acromegalic patients, intra-abdominal fat increases. Visceral obesity is a risk factor for cardiovascular disease. Hence, confirmation and further studies in a larger cohort of acromegalic patients on PEG treatment are warranted.

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Introduction

Somatostatin analogs (SSA) are the primary medical treatment for acromegaly. However, for patients responding insufficiently to SSA, the use of the growth hormone (GH) receptor blocker pegvisomant (PEG) is recommended (1). These two drugs have different effects on lipid and glucose metabolism. Due to the excess GH, untreated acromegaly is associated with increased lipolysis, decreased fat mass, insulin resistance (IR), and deterioration of glucose tolerance (GT). During SSA therapy, insulin that facilitates lipolysis is suppressed by the drug (2). Hence, patients on SSA still have a decreased fat mass and glucose intolerance even if GH is normalized. By contrast, during PEG therapy, GH no longer stimulates lipolysis due to the blockade of its receptor, while insulin action is unabated. Therefore, insulin sensitivity should improve and fat mass, including intra-abdominal fat, should increase. Visceral obesity is associated with an increased cardiovascular risk (3, 4). We therefore investigated intra-abdominal

fat mass and insulin sensitivity in five acromegalic patients, who had insufficiently responded to depot-octreotide (OCT) therapy, before and during PEG therapy. They were studied after at least a 3-month OCT-washout period (baseline) and again after 6 months on PEG therapy.

Patients and methods

We performed a prospective, non-randomized, open study with three female and two male patients, median age 51 years (range 45–73; Table 1). All had active acromegaly and had been on a stable dose of OCT. The dose and the median duration (range) of OCT treatment were 30 mg every 4 weeks for 8.9 (2.9–16.8) years. During OCT treatment, all patients had failed to fulfill the criteria for biochemical cure of acromegaly (suppression of GH below 1.0 µg/l during an oral glucose load and age-adjusted normal insulin-like growth factor-I (IGF-I) concentration (5)). Patients were taken off OCT and

Table 1 Patients' characteristics.

Patient	Age (years)	Sex	Diagnosis (year)	Surgery (year)
1	46	F	1986	1986
2	52	F	1986	1999
3	73	M	1991	1991
4	45	M	1999	1999
5	73	F	1986	1992

F, female; M, male.

studied at the end of a 3-month washout period (baseline study). PEG was started at 10 mg/d s.c., and the dose was adjusted every 4 weeks, up to a maximum of 25 mg/d, in order to achieve a serum IGF-I concentration within the age-adjusted normal range. The study protocol was repeated after 6 months on PEG. Substitution therapy was maintained on a stable dose throughout the investigation, with three patients on hydrocortisone, three on L-thyroxine, and one on testosterone. Additional medication, consisting of angiotensin-converting enzyme inhibitors (*N* = 3), hydrochlorothiazide (*N* = 1), and calcium and vitamin D supplementation (*N* = 3) was kept stable throughout.

All tests were performed after an overnight fast. Insulin sensitivity was estimated by a homeostatic model assessment (HOMA-IR value) and by hyperinsulinemic euglycemic clamp (*M* value). HOMA-IR was calculated from fasting insulin (mIU/l) and glucose (mmol/l) concentrations by a correctly solved computer model (6) for predicting IR (6–9). HOMA-IR values have been shown to correlate with IR obtained by hyperglycemic and euglycemic clamps (10, 11).

For the hyperinsulinemic euglycemic clamp, the subjects were in a supine position with the upper body lifted ~30° throughout the experiments. The forearm was placed in a heating system maintaining a temperature of 50 °C in order to obtain arterialized venous blood samples. The patients received a primed insulin infusion at a rate of 2.0 mU/kg × min^{−1} for 3 h. A C-peptide concentration below the assay sensitivity indicated a complete suppression of endogenous insulin secretion. Blood was drawn every 10 min for the determination of blood glucose, insulin, and C-peptide. IGF-I was determined in the first sample. The infusion rate of exogenous glucose was adjusted to maintain a glucose concentration of 90 mg/dl (5.04 mmol/l). The insulin sensitivity for the systemic glucose uptake was calculated as mean infusion rate of glucose necessary to maintain euglycemia during the last 60 min of the euglycemic clamp (*M* value: mg glucose × kg^{−1} × min^{−1}).

Blood was centrifuged immediately after withdrawal. Serum for hormone determinations was kept at −25 °C until assayed in duplicate as one single batch. The following assays were used: insulin and C-peptide by chemiluminescence enzyme immunoassays (Biermann, Bad Nauheim, Germany and Biochem Immuno Systems, Bologna, Italy, resp.) and IGF-I by RIA-CT

(Mediagnost, Reutlingen, Germany). Assay sensitivity, intra- and inter-assay variation coefficients were 2 µU/ml, 6.0% and 5.3% for insulin; 0.1 ng/ml, 3.34% and 3.23% for C-peptide; and 0.107 ng/ml, 7.2% and 8.6% for IGF-I. Glucose was determined by a glucose dehydrogenase method (HemoCue, Grossostheim, Germany). Total cholesterol and high-density lipoprotein (HDL) cholesterol were determined photometrically and low-density lipoprotein (LDL) cholesterol was then calculated as total cholesterol minus HDL cholesterol minus (triglycerides/5) according to Friedewald (12). Intra-abdominal and s.c. fat mass were determined by electron beam computed tomography (Imatron C150, Imatron, San Francisco, CA, USA) with axial abdominal slices (3 mm) at L2 of the lumbar spine, using numerical analysis of the fat distribution.

Statistical analysis

For a description of the data, the mean ± s.e.m. or median (min–max) were used whenever appropriate. Comparisons were calculated using paired *t*-test or Wilcoxon's test for paired samples. Statistical significance was accepted at *P* < 0.05.

Informed written consent was obtained from all patients. The study was performed in agreement with the Declaration of Helsinki and the general outlines of the good clinical practice (GCP). The study protocol was approved by the hospital Ethical Committee.

Results

IGF-I concentration

At the end of the washout period, the IGF-I concentration was elevated in all five patients. After 6 months on PEG, IGF-I was reduced to within the age-adjusted normal range in all patients (Table 2).

Table 2 Insulin-like growth factor-I (IGF-I) concentration (individual values and age-adjusted normal range).

Patient	Baseline (off octreotide) ^a	Pegvisomant	Normal range ^b
1	565	227	(103–307)
2	772	206	(97–294)
3	566	127	(91–284)
4	593	243	(103–307)
5	376	140	(91–284)
Mean ± s.e.m.	574 ± 125.6	189 ± 52.2	
<i>P</i> value		<0.03	

^aAfter 3 months of OCT washout, before PEG therapy.

^b5–95th percentile of the normal, age-adjusted range.

Table 3 Fat mass (cm²), individual, and median values and ratio abdominal/s.c. fat.

Patient	Intra-abdominal fat		S.c. fat		Ratio intra-abdominal/s.c. fat	
	Baseline ^a	Pegvisomant	Baseline ^a	Pegvisomant	Baseline ^a	Pegvisomant
1	112	172	257	284	0.44	0.61
2	84	112	145	162	0.58	0.69
3	480	524	286	229	1.68	2.29
4	160	226	206	202	0.78	1.12
5	88	156	182	244	0.48	0.64
Median	112	172	206	229	0.58	0.69
Range	(84–480)	(112–524)	(145–286)	(162–284)	(0.44–1.68)	(0.61–2.29)
P value		<0.05		NS		<0.05

^aDuring 3 months of OCT washout, before PEG therapy.

Intra-abdominal and s.c. fat

The intra-abdominal fat mass increased significantly during PEG therapy ($P < 0.05$) compared with baseline, as did the ratio intra-abdominal/s.c. fat. The s.c. fat mass also increased but to a lesser degree and this change was not significant (Table 3).

IR and glucose metabolism

The median values for HOMA-IR and the *M* value (clamp studies) were not significantly different between baseline and PEG (Table 4). Analyzed individually, the HOMA-IR value decreased slightly in three (indicating increased insulin sensitivity) and increased in two patients. The *M* value as well increased slightly in three patients (again indicating higher insulin sensitivity) and decreased slightly in two patients compared with baseline. Thus, overall on PEG treatment, the indices of glucose metabolism were not uniformly and significantly different from baseline, i.e., from untreated acromegaly.

Plasma cholesterol and triglycerides

LDL cholesterol, HDL cholesterol, and triglycerides were slightly higher during PEG therapy, but the LDL to HDL ratio improved slightly from 3.25 ± 0.78 to 2.83 ± 0.36 . However, these differences were not significant (Table 5).

Discussion

PEG therapy effectively normalized IGF-I in all five patients, as has been previously shown by others (13).

Table 4 Glucose sensitivity data (median, min–max).

	Baseline ^a	Pegvisomant	P
HOMA	3.11 (0.74–4.65)	2.81 (0.51–5.10)	NS
<i>M</i> value (clamp)	2.14 (0.63–8.78)	2.30 (0.56–9.26)	NS

^aDuring 3 months of OCT washout, before PEG therapy.

It also significantly increased their intra-abdominal fat mass. Untreated acromegalic patients have a decreased fat mass due to the lipolytic effect of GH. Increased lipolysis also causes IR and deterioration of GT. If GH is normalized by a surgery, the increased lipolysis will disappear and the fat mass, insulin sensitivity, and GT will subsequently normalize. However, if GH is normalized by SSA therapy, the drug-induced suppression of insulin secretion, directly and via suppression of GLP-1 (2), increases lipolysis. Hence, the decreased fat mass and glucose intolerance persist, but they are now drug induced. By contrast, during PEG therapy, GH no longer stimulates lipolysis due to the blockade of its receptor, while insulin action is unabated. Therefore, insulin sensitivity should improve and fat mass, including intra-abdominal fat, should increase. Thus, our finding of increased fat mass is compatible with the known mode of action of PEG. It could be argued that the increase of intra-abdominal fat may be partly time or age related. However, the age-related increase (between 35 and 74 years) in fat mass index (kg/m²) is only 0.012 and 0.028 per 6 months in healthy male and female subjects respectively (14). Hence, it is much too small to explain a substantial part of the observed increase in our patients.

There was also a slight increase of s.c. fat, but this was not significant. S.c. fat is less important than visceral fat for IR and as a cardiovascular risk factor (15, 16). The preponderance of the increase of visceral over s.c. fat may be due to locally increased 11 β -hydroxysteroid dehydrogenase (11 β HSD-I) activity. The type-I isoform of 11 β HSD-I that converts cortisone to cortisol is more concentrated in visceral than in s.c. fat. 11 β HSD-I is inhibited by GH (17). The increased local 11 β HSD-I

Table 5 Lipid concentrations (mean $\pm$ S.E.M., mmol/l).

	Baseline ^a	Pegvisomant	P
LDL cholesterol	3.56 ± 0.44	3.74 ± 0.21	NS
HDL cholesterol	1.26 ± 0.10	1.42 ± 0.18	NS
Ratio LDL/HDL ^b	3.25 ± 0.78	2.83 ± 0.36	NS
Triglycerides	1.67 ± 0.27	1.90 ± 0.40	NS

^aDuring 3 months of OCT washout, before PEG therapy.^bMean of individual ratios.

activity due to the lack of GH-induced inhibition may be a factor in the more pronounced increase of visceral when compared with s.c. fat during PEG therapy (18).

Contrary to expectation, our patients showed no significant improvement of GT. This is in contrast to the finding of Colao *et al.* (19) who also studied acromegalic patients during PEG therapy following an OCT washout. On the other hand, our findings are in line with the results demonstrating either unaffected or even diminished GT during short-term PEG treatment of healthy subjects (20–22). Moreover, it appears that the improvement of GT during PEG therapy is variable and more pronounced in patients with the poorest GT prior to PEG therapy (19, 23). However, an improvement of GT may have been masked in our study by the small number of patients, three of whom had an amelioration and two a deterioration of GT. Two other studies that have also found improved GT during PEG therapy (23, 24) are not compatible. In these studies, the comparison was made between GT during OCT and PEG therapies respectively rather than after an OCT washout and PEG therapy. OCT suppresses insulin secretion (2, 25). Therefore, GT will be poor even in the presence of normalized GH concentrations. PEG, on the other hand, has no effect on the insulin secretion and hence the removal of GH-induced IR by the GH receptor blockade diminishes lipolysis. Thus, an improvement of GT is to be expected when a patient is directly transferred from OCT to PEG therapy.

We found increased visceral obesity but no improvement of GT, although our patients had normal IGF-I concentrations. We speculate that this combination could also alternatively point to the development of GH deficiency (GHD) during PEG therapy. GHD may be present despite a normal IGF-I concentration (26). It is also known that GHD causes IR (27, 28). In a model of PEG-induced GHD (in healthy adults), IR developed in the liver and the muscle but not in the adipose tissue (20). PEG-induced GHD would therefore be compatible with a combination of increased obesity and glucose intolerance. However, this speculation needs to be investigated by further studies.

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