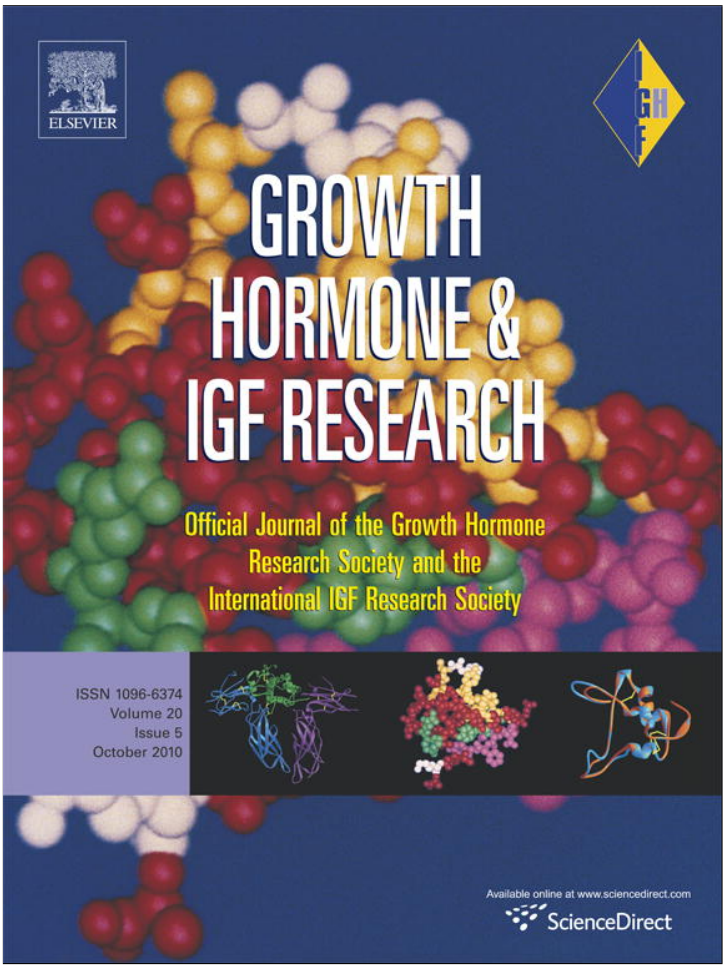

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The acute effect of a single application of cabergoline on endogenous GH levels in patients with acromegaly on pegvisomant treatment ☆

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ABSTRACT

Objective: Treatment with pegvisomant, an antagonist of growth hormone (GH) receptors, increases GH levels in a dose dependent manner. Cabergoline can suppress GH secretion in approximately 40% of acromegalic patients. However, the acute effects of cabergoline have not been studied in patients treated with pegvisomant. We performed this cross-sectional study to evaluate endogenous GH after an additional single cabergoline administration.

Design: 9 acromegalic patients on pegvisomant therapy were included. A 6 h GH profile after pegvisomant alone (P) and a 9 h profile in combination with oral cabergoline 0.5 mg (PC) were performed. After 3 or 6 h, all patients received a standardized light mixed meal. Endogenous serum GH and pegvisomant levels were measured by special in-house assays. The GH assay showed no interference with pegvisomant.

Results: Endogenous GH levels at baseline did not differ significantly between the profiles (P: 16.5 μg/l (range 3.2–36.6 μg/l), PC: 8.0 μg/l (1.6–48 μg/l), $p>0.05$). In both profiles, GH fluctuated before meal. GH decreased more pronounced in PC but this decrease was not statistically significant. After meal, a significant decline in endogenous GH levels from 16.4 μg/l (0.4–27.1 μg/l, 100%) to 8.1 μg/l (0.2–24.7 μg/l, 66%) appeared in P at 300 min ($p<0.01$). Also in PC a decline from 7.8 μg/l (1.1–29.6 μg/l, 100%) to 5.2 μg/l (0.4–23.9 μg/l, 75%) at 300 min was observed but it was not significant.

Conclusion: Endogenous GH is not significantly decreased after a single oral cabergoline application during pegvisomant treatment in acromegaly.

1. Introduction

Pegvisomant, a recently developed drug for the treatment of acromegaly, is a recombinant human growth hormone [1]. Due to a single amino acid substitution at position 120, pegvisomant antagonises GH receptors [2,3]. It normalizes IGF-I levels in 75–90% of acromegalic patients [4,5], but causes a dose dependent increase due to the blockade of peripheral GH receptors [4,6]. Measurement of endogenous GH levels during pegvisomant therapy is problematic as most conventional assays interfere with the drug [1]. Special assays have been developed to eliminate any interference and cross-reactivity with the drug [2,7]. However, not a lot is known about endogenous GH during pegvisomant therapy. It has been reported that GH levels can be reduced by somatostatin analogues acutely [8] and after long term co-treatment [9]. Furthermore, it seems to be normally regulated by food intake [8]. The kinetics of GH removal were shown to be unaffected by pegvisomant at least in healthy humans [10].

A few studies have been conducted so far to investigate the combined treatment of pegvisomant with somatostatin analogues [9,11,12], which are the first line therapy in the treatment of acromegaly [13]. The combined treatment seems to be more effective in normalizing IGF-I levels than either drug alone [9]. Furthermore, co-treatment with somatostatin analogues counterbalances the increase of endogenous GH levels caused by pegvisomant therapy [9].

Cabergoline is an ergot derivate which binds highly selective to the subtype D2 of the dopamine receptor [14]. It is an effective and well tolerated therapy in acromegaly, especially in GH and prolactin co-secreting adenoma [15]. However, not all studies showed a higher effectiveness of cabergoline in co-secreting tumors [16]. GH is described to be reduced by approximately 35% [16] to 47% [17] during cabergoline monotherapy. Another study showed in 7 out of 10 patients a decrease of

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GH to < or = 33% [18]. Moreover, studies have investigated the combined treatment of cabergoline and somatostatin analogues and found a higher GH reduction compared to a single therapy [19–22].

Only very few data exist about the combined treatment of pegvisomant and a dopamine agonist [23,24].

We conducted this cross-sectional study on 9 acromegalic patients on pegvisomant therapy to evaluate the characteristics of endogenous GH after a single acute application of the dopamine agonist cabergoline. We were interested whether the combination of cabergoline and pegvisomant might be effective in reducing endogenous GH during pegvisomant therapy. Furthermore, we compared the changes in endogenous GH levels after a light mixed meal during only pegvisomant and during the combination with cabergoline to evaluate whether the physiological decrease of GH by food is remained.

2. Patients and methods

2.1. Patients

We asked all patients with acromegaly currently on pegvisomant treatment attending our outpatient clinic to participate in this cross-sectional study. 7 patients (3 females and 4 males) gave informed consent to attend and were included into this study. 3 patients refused to participate. Furthermore, 2 patients of the Max-Planck-Institute of Psychiatry (Department of Endocrinology, Munich, Germany) were included into this study after giving informed consent (1 female and 1 male). The investigation was reviewed and approved by the Ethics Committee of the Medical Faculty of the LMU Muenchen as well as by the Federal Institute of drugs and medical devices. Median age of the patients was 50 years (range 42–65). All patients had undergone transsphenoidal surgery, 7 patients had received additional conventional radiotherapy. 6 patients were previously on dopamine agonist therapy and all patients were on somatostatin analogue therapy before. 3 patients had type II diabetes mellitus, 2/3 patients were treated with diet and glucophage (metformin®), 1/3 of patients was treated with insulin and was therefore excluded from statistical evaluation of blood glucose and insulin.

Median duration of pegvisomant treatment before study entry was 7 months (range 4–35) with a median dose of 10 mg (range 10–30 mg). All patients had an IGF-I level within the age- and sex-adjusted reference value [25] and were therefore defined as in remission. For more patients' characteristics before study entry please see Table 1.

2.2. Methods

2.2.1. Profiles

All patients were examined on two different days after overnight fasting. The interval between the two examinations was at least one week. Either a 6 or a 9 h profile was performed. At the beginning of each profile, basal blood samples were taken for haematology, clinical chemistry and endocrine diagnostics.

2.2.2. Profile P (P)

After the basal blood sample was taken, all patients injected pegvisomant subcutaneously in their individual dose. Blood samples for endogenous serum GH, pegvisomant, insulin and glucose were taken during 6 h at the time points 0 min, 30 min, 60 min, 120 min, 180 min, 240 min, 300 min, and 360 min. After 180 min all patients received a standardized light mixed meal consisting of 79.9 g carbohydrates, 29.2 g proteins and 38.8 g fat.

2.2.3. Profile PC (PC)

Profile PC was performed according to profile P but lasted for 9 h. 3 h before pegvisomant injection, patients received cabergoline 0.5 mg orally. Cabergoline application was set 3 h before pegvisomant injection because its peak plasma concentration is reached after 2–3 h [26]. In addition to the blood samples for endogenous serum GH, pegvisomant, insulin and glucose, prolactin was measured in order to quantify the effect of cabergoline. Blood samples were taken during 9 h at the time points −180 min, −120 min, −60 min, 0 min, 30 min, 60 min, 120 min, 180 min, 240 min, 300 min, and 360 min. After 360 min, at time point 180 min, again all patients received a standardized light mixed meal in accordance to profile P.

2.2.4. Laboratory values

IGF-I concentrations were measured using an automated chemiluminescent immunoassay (Immulite®, Diagnostic Products Corporation, Los Angeles, CA, USA). Immulite® IGF-I is a two-site, solid-phase, chemiluminescent enzyme immunometric assay and is standardized according to the World Health Organisation's 2nd IS 87/518 [27]. IGF-I is given as the multiple of age- and gender-adjusted upper limit of normal (xULN) with reference to the published normative data for this method [25].

In order to monitor endogenous GH secretion in patients treated with the GH-analogue pegvisomant, a specific assay was designed, which was free of interference by the drug. The assay has been validated and is described in detail elsewhere [2,10,28]. In brief, from a panel of monoclonal antibodies (mAbs) raised against GH, a pair of antibodies was identified targeting epitopes in receptor binding sites 1 and 2, respectively, which have been mutated in the GH-analogue. Neither of the mAbs selected showed cross-reaction with pegvisomant, indicating that they target amino acid residues mutated in pegvisomant. Combining these antibodies (named 8B11 and 6C1) in a sandwich-assay leads to a linear dose–relationship for GH with a lower detection limit of 0.2 μg/l and an upper end of the linear working range at 50 μg/l for 50 μl samples. WHO IRP 80/505 is used as the calibrator. Intra-assay variability was 4.1% and 3.9% at concentrations of 5.2 μg/l and 14.6 μg/l, respectively. Inter-assay variability at

Table 1
Patients' characteristics at study entry.

Patient	1	2	3	4	5	6	7	8	9
Sex	F	F	F	M	M	F	M	M	M
Age (years)	50	43	54	42	46	44	65	63	53
BMI (kg/m^2)	33	28	31	26	29	32	26	29	29
xULN (IGF-I)	0.7	0.5	0.9	1.0	0.7	1.0	0.7	0.6	0.5
Pituitary deficiency (n)	2	3	1	2	0	2	1	3	1
Radiotherapy (year)	2000	1998, 2002, 2004	No	2002	2004	1986	1995	1978	no
Peg duration (months)	7	35	35	6	24	16	6	5	4
Peg dose (mg/day)	10	30	30	15	10	20	10	10	10
Previous DA	No	No	BC	QG	CG	BC	BC	BC	No
D.m.	Yes	No	No	No	No	No	Yes	Yes	No
Time of D.m.	>10 years						2000	>10 years	
Medication of D.m.	Glucophage since 2003						Glucophage since 2003	Insulin since 2001	

peg = pegvisomant, DA = dopamine agonist therapy, BC = bromocriptine, QG = quinagolide, CG = cabergoline, D.m. = Diabetes mellitus II, and time = date of first diagnosis.

the same concentrations was determined to be 7.3% and 9.2%, respectively.

Serum concentrations of pegvisomant were determined by an immunofluorometric sandwich type assay involving two monoclonal antibodies directed against GH and retaining high cross-reactivity with PEGylated pegvisomant (25–50% compared to wt rhGH). The assay was calibrated against pegvisomant (Pfizer, NY) diluted in assay buffer. Serum concentrations of pegvisomant in treated patients are by a factor of at least 500 higher than endogenous GH concentrations. Therefore, all serum samples were diluted 1:100 in assay buffer prior to analysis to eliminate the interference from the endogenous GH levels present in the samples. The assay has a linear working range from 0.5–200 μg/l, corresponding to final concentrations of 50–20,000 μg/l. Samples above 200 μg/l have been diluted in assay buffer, samples below 0.5 μg/l (corresponding to a final concentration of 50 μg/l) have been reported as "<50 μg/l". The intra-assay variability was 7.5, 4.6 and 5.2% at concentrations of 160, 650 and 3900 μg/l, respectively. The inter-assay variability was 13.5, 6.4 and 8.5% at the same concentrations.

Prolactin was analysed using an immuno-chemoluminescent assay (Bayer Centaur). Glucose levels were measured by an automated glucose analyser (Care Eco solo I, Care Diagnostic); Insulin levels were determined by a radioimmunoassay (Adaltis Italia, S.p.A; Casalecchio di Reno, Italy). HbA1c levels were analysed from whole blood, standardized to IFCC and calculated according to DCCT/NGSP (Integra 700, Roche, Switzerland).

2.2.5. Statistical analysis

SPSS (version 16.0) was used for data analysis. Data were expressed as median and range, due to their non-normal distribution. First, possible significant differences during profiles were calculated by Friedman-test for related measurements. If significant differences could be evaluated, non-parametric Wilcoxon signed-range test for related measurements was used for comparison of two variables. The area under the curve (AUC) was calculated by the trapezoidal rule.

Profiles were separated into two phases for further evaluation. Phase 1 run from time point 0 min to time point 180 min in profile P and from time point −180 min to 180 min in profile PC. This is the time period before meal. Phase 2 spanned from meal time (at 180 min) to the end of the profile. The baseline levels and the level at 180 min were set at 100%. The following GH levels are given as percentage of the baseline or 180 min levels, respectively. The GH decline before meal was calculated by the difference from baseline to the mean of 30 min to 180 min.

GH and prolactin nadir as well as glucose and insulin peaks were determined at time points when most of the patients had reached their minimum or maximum level, respectively.

A p-value <0.05 was considered as the nominal level of significance.

3. Results

Median xULN of IGF-I (xULN) before study entry was 0.7 (range 0.5–1.0). All patients had a xULN ≤ 1, which was defined as in remission. Median BMI for all patients was 29 kg/m^2 (26–33 kg/m^2), median HbA1c 6.0% (5.4–7.2%).

3.1. Endogenous GH levels

Fig. 1 shows the effects on endogenous GH levels. Baseline level and time point 180 min were set at 100%. Endogenous GH levels at baseline did not differ significantly between the two profiles (P: 16.5 μg/l (range 3.2–36.6 μg/l), PC: 8.0 μg/l (1.6–48 μg/l), $p>0.05$). In both profiles, GH fluctuated much before meal. In profile P, a statistically significant decrease with the minimum at time point 120 min (14.9 μg/l (range 0.3–25 μg/l) $p<0.01$) could be calculated. In profile PC, no significant decrease occurred for any of the patients. Looking at each single patient, a GH decline >30% could be observed in 3 patients in profile P and in 4 patients in profile PC. The AUC of GH before meal was not significantly different between the profiles (P: 2834 μg min/l (170–5079 μg min/l), PC: 1343 μg min/l (216–5510 μg min/l); $p>0.05$).

After meal, a significant decline in endogenous GH levels from 16.4 μg/l (0.4–27.1 μg/l) to 8.1 μg/l (0.2–24.7 μg/l) appeared in profile P with a maximum at 300 min ($p<0.01$). This decline was seen in all patients with a median percentage decline of 33.5% (3.2–66.7%). Also in PC, a slight decline from 7.8 μg/l (1.1–29.6 μg/l) to 5.2 μg/l (0.4–23.9 μg/l) at 300 min was observed but this decrease was not significant ($p>0.05$). The AUC of GH after meal was not significantly different between the profiles (P: 2196 μg min/l (45–7509 μg min/l), PC: 1305 μg min/l (168–4584 μg min/l); $p>0.05$).

3.2. Prolactin levels

In Fig. 2 the run of prolactin is shown. Prolactin at baseline was 143 mU/l (0.1–694 mU/l). It decreased significantly to 53.4 mU/l (0.1–452.7 mU/l) during the first 3 h and then further decreased to 48 mU/l (0.1–453.6 mU/l) during the next 30 min. The median percentage decline was 66% (0–81%). For the rest of the profile prolactin levels did not further change significantly. The AUC of prolactin was significantly different for the first 3 h (15630 mU min/l (18–99747 mU min/l)) compared to the second 3 h (8924 mU min/l (288–81615 mU min/l), $p<0.05$) as well as to the last 3 h (12225 mU min/l (21–79173 mU min/l), $p<0.05$) but did not differ significantly between the second 3 h and the last 3 h after meal ($p>0.05$).

3.3. Pegvisomant levels

Baseline pegvisomant levels before pegvisomant injection did not differ significantly between profile P and profile PC (P: 7507 μg/l (2950–14900 μg/l), PC: 6950 μg/l (1310–22913 μg/l), $p>0.05$). Furthermore, pegvisomant levels did not change significantly during both profiles ($p>0.05$). At no time point during the profiles, a significant difference in pegvisomant levels could be observed between the two profiles ($p>0.05$).

3.4. Glucose levels

In Fig. 3 glucose levels during P and PC are illustrated. Basal blood glucose levels were not significantly different for profile P (84 mg/dl (68–104 mg/dl)) and PC (82 mg/dl (66–109 mg/dl); $p>0.05$). They only fluctuated slightly before the meal. But after meal, glucose levels rose significantly from 85 mg/dl (66–97 mg/dl) to 141 mg/dl (124–202 mg/dl) during profile P ($p<0.05$) and from 72 mg/dl (65–87 mg/dl) to 116 mg/dl (93–133 mg/dl) during PC ($p<0.05$). Peak glucose concentrations were reached at time point 240 min in both profiles. The rise in glucose levels after meal was significantly higher for profile P compared to profile PC ($p<0.05$). Moreover, glucose levels at 240 min were higher for P ($p<0.05$). AUC of glucose before and after meal was higher for profile P than for profile PC (before meal: P: 15308 mg min/dl (12795–19050 mg min/dl), PC: 13500 mg min/dl (12525–15420 mg min/dl), $p<0.05$; after meal: P: 21195 mg min/dl (18270–28350 mg min/dl), PC: 19155 mg min/dl (15780–24960 mg min/dl), $p<0.05$).

3.5. Insulin levels

Fig. 3 demonstrates insulin levels during the two profiles. Baseline insulin concentrations did not differ significantly for the two profiles (P: 13.3 μU/l (3.5–25 μU/l), PC: 8.8 μU/l (4.2–19.8 μU/l), $p>0.05$). Insulin levels did not fluctuate much before meal in both profiles. After the meal, there was a significant increase in insulin levels from 6.8 μU/l (3–22 μU/l)

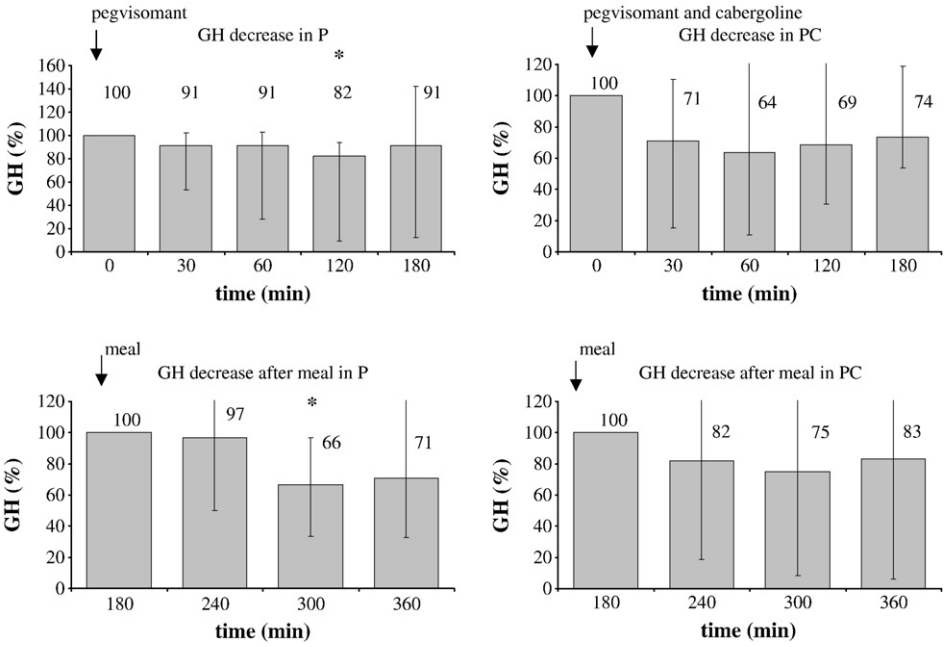

Fig. 1. Endogenous GH fluctuated much before meal time in both profiles. In profile pegvisomant alone, GH statistically significant decreased with a minimum at 120 min ($p<0.01$). In the combined profile pegvisomant and cabergoline, no significant decrease of endogenous GH appeared. After meal, endogenous GH significantly decreased with a nadir at 300 min only in profile P ($p<0.01$). Values are given as percentage of the baseline levels and the level at 180 min, which were set at 100%. Values were given in median and range. * = $p<0.01$.

to 89.3 μU/l (8.2–224 μU/l, $p<0.05$) in P and from 6.1 μU/l (3.3–22 μU/l) to 51.3 μU/l (11.2–104 μU/l, $p<0.05$) in PC with a maximum at 240 min in both profiles. Maximum insulin levels at 240 min and the amount of rise were not significantly different between P and PC ($p>0.05$). In accordance, the AUC of insulin before (P: 1424 μU min/l (752–3825 μU min/l), PC: 1247 μU min/l(767–2523 μU min/l), $p>0.05$) and after the meal (P: 11741 μU min/l (3291–19050 μU min/l), PC: 8178 μU min/l (2742–23754 μU min/l), $p>0.05$) was not significantly different for both profiles.

4. Discussion

Our main result in this study was that endogenous GH did not decrease in acromegalic patients on pegvisomant therapy after co-treatment with cabergoline. After pegvisomant alone, a slight but statistically significant decline was calculated at one time point. In 3 patients after pegvisomant alone and in 4 patients after the combination with cabergoline, a GH decline>30% could be observed. It is unclear whether this decline is actually a result of the treatment and these patients are dopamine agonist responders or if it is due to the well known fluctuation of GH levels during daytime.

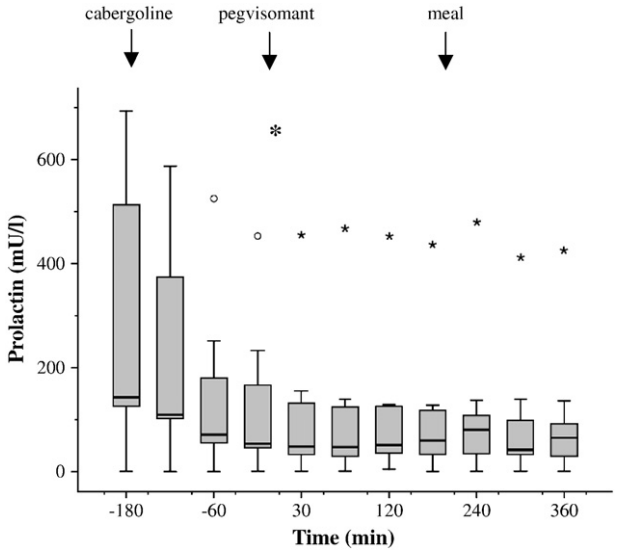

Fig. 2. Prolactin significantly decreased with a nadir at 30 min ($p<0.05$). For the rest of the profile, prolactin did not further change significantly ($p>0.05$). Values are given in boxplots showing median and range. * = $p<0.05$.

To our knowledge no data exist so far about the behaviour of endogenous GH after dopamine agonist administration in pegvisomant treated acromegalic patients. Data of the combined treatment are only given in one original article and an abstract. The article published the knowledge about pegvisomant as a treatment for acromegaly. It was noted that two patients in which a reduction of IGF-I had been achieved with cabergoline alone pegvisomant was added as an attempt to reduce pegvisomant dose and the cost of treatment. No further information, such as GH levels, are given in the article [24]. The abstract shown at the meeting of the Endocrine Society demonstrated data of a prospective clinical trial exploring the combination on 24 patients [23]. IGF-I levels were significantly lower during combined treatment compared to each monotherapy. But again no data of GH levels are given.

In general, little is known about endogenous GH during pegvisomant treatment. In order to measure only endogenous GH, it has to be measured with special assays without interference and cross-reactivity with pegvisomant [2,7]. GH increases after starting pegvisomant therapy in acromegaly and then plateaus in a dose dependent manner [4,6]. Moreover, somatostatin analogues can reduce endogenous GH during pegvisomant therapy acutely [8] and after long term co-treatment [9].

A GH decline after the combined treatment would have been expected as already cabergoline monotherapy is known to reduce GH in acromegaly [15,16,18] by approximately 35% [16] or 47% [17] after long term treatment. A single administration of cabergoline has been shown to decrease mean GH by 42% in 8 dopamine responsive patients [29]. In addition, cabergoline given in combination to somatostatin analogues is able to further reduce GH as much as 70% [19] to 88% [22] compared to somatostatin analogue monotherapy [19–22]. Furthermore, a few studies have been performed

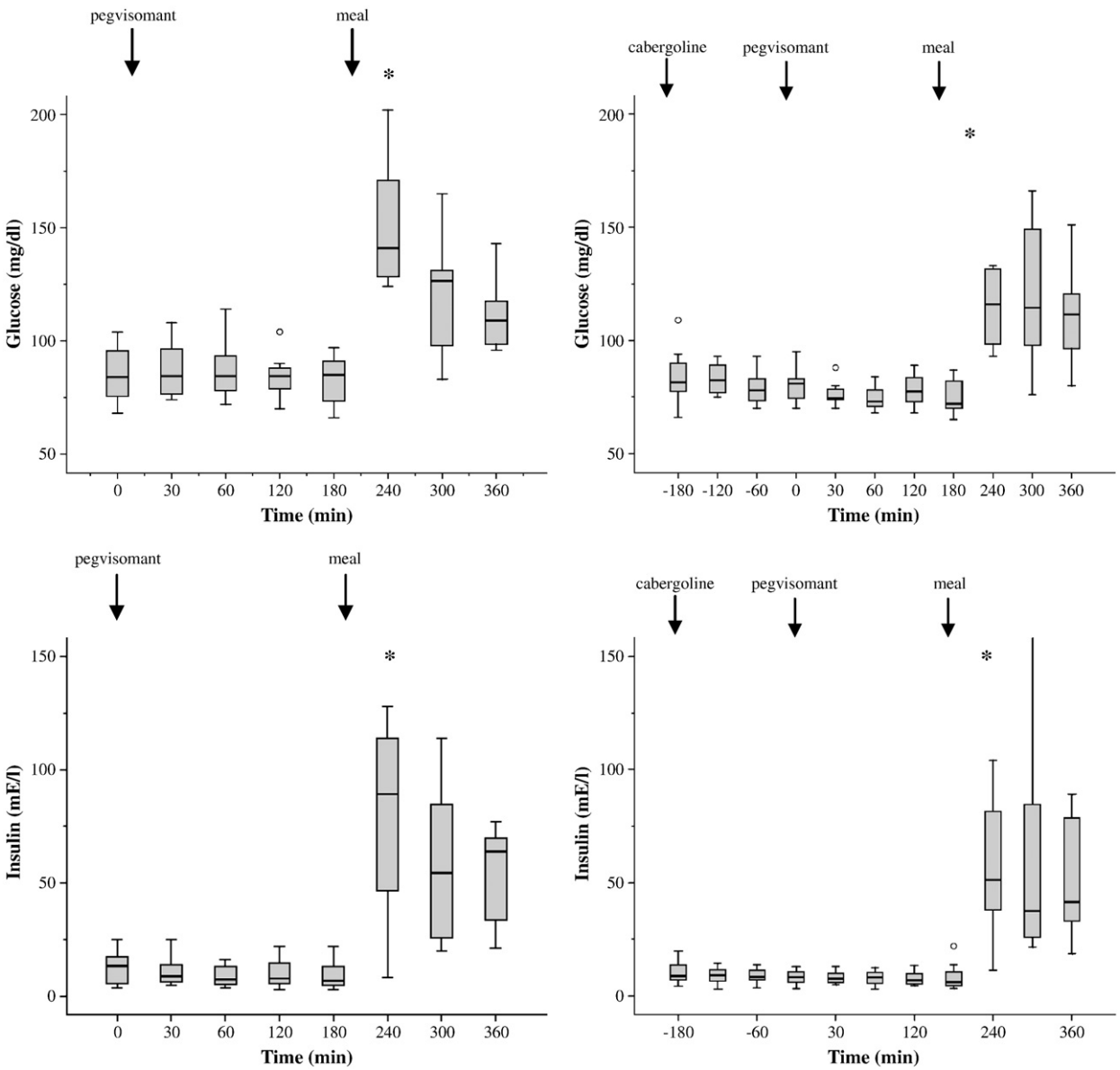

Fig. 3. Basal blood glucose and insulin levels were not significantly different for profiles P and PC ($p>0.05$). Glucose and insulin levels rose significantly after meal with a maximum at time point 240 min in both profiles ($p<0.05$). The rise in glucose levels after meal was significantly higher for profile P compared to profile PC ($p<0.05$), whereas the insulin increase was not significantly different ($p>0.05$). Values are given in boxplots showing median and range. * = $p<0.05$.

investigating the combined treatment of pegvisomant and somatostatin analogues [9,11,12]. In one of these studies endogenous GH was measured, showing a decrease in endogenous GH from 19.7 μg/l during pegvisomant monotherapy to 11.8 μg/l after additional somatostatin analogue application (60%) [9]. In our patients, endogenous GH did not decrease significantly after combined treatment in all patients. First, it has to be mentioned that most of the published data on GH decline after cabergoline treatment are long term treatment data, whereas our data were only after a single cabergoline administration. However in one publication on 21 patients a single cabergoline application suppressed GH by more than 50% in 5 acromegalic patients (24%) [21]. Furthermore, the above mentioned study showing a 42% reduction of GH was performed on 8 dopamine responsive patients [29], whereas our patients could not be controlled by dopamine agonists alone in the past. Taking this into account, a reason for the missing GH responds after cabergoline might be that our patient population consisted of special therapy resistant acromegalic patients as none of them could be controlled by surgery and dopamine agonist or somatostatin analogue monotherapy. We included 3 patients with diabetes and 7 patients treated with radiotherapy. As diabetes and radiotherapy are known to influence GH levels these patients are not the ideal cohort to answer the study question. It is well known that in diabetic patients with poorly controlled glucose levels GH levels are higher and the physiological suppression of GH by glucose is reduced [30,31]. In acromegalic patients with poorly controlled diabetes GH levels might also be influenced and GH regulation after food intake might be altered. As three of our investigated patients had diabetes this could have influenced GH levels and secretion during our profiles. However, as the highest HbA1c was 7.2%, glucose metabolism seems to be well controlled. The influence on GH levels should be minor. Still this might have influenced our results. Data have shown a significant discrepancy between the reduction of GH and IGF-I levels after pituitary irradiation [32]. The reason for the lack of normalisation of IGF-I levels

despite low GH levels remains unclear. Some authors speculated that it might reflect the maintenance of GH pulsatile secretion after irradiation, which is able to stimulate hepatic IGF-I production, even with normalized GH levels [33]. However, it might be possible that the GH physiology is destructed after radiotherapy. In our patients the GH physiology seems at least partly maintained as glucose intake leads to a decrease in GH levels and GH fluctuates during the two profiles. Moreover, this study was performed on a group of only 9 patients, which might be too small to get significant results. The small and not ideal patient population examined in this study was due to the generally low number of acromegalic patients on pegvisomant treatment.

Endogenous GH decreased significantly after food intake with a median percentage decline of 33.5% and a nadir at 2 h after only pegvisomant application. After co-treatment with cabergoline, a slight decrease was visible but this decrease was not significant. GH levels after food intake decrease because of a food induced glucose rise which stimulates endogenous somatostatin [34]. Somatostatin inhibits GH secretion and leads to a reduction in GH levels. Therefore, our results suggest that the physiological regulation of endogenous GH by food intake seems to be maintained during pegvisomant therapy as it has been previously reported by our group [8]. An explanation for the lack of significant change after cabergoline treatment might be that glucose levels during the combined profile were lower and glucose levels did increase less after food intake compared to the profile with pegvisomant alone. Therefore, the stimulating influence of glucose rise on endogenous somatostatin might have been reduced. Reasons for lower glucose levels during the combined profile may be that the dopamine agonist cabergoline itself might have an anti-glucogenic effect [35–37]. Moreover, cabergoline reduces prolactin by binding to dopamine receptors D2 [14]. Prolactin is a glycogenic hormone [38]. Therefore, its suppression itself, which was in median 66% in our patients, might have reduced glucose levels. In our cohort insulin levels were not significantly different between both treatment regimes, nor were the insulin rises after food intake significantly different. This is in accordance to previously published studies which did not show changes in insulin levels after dopamine agonist therapy [35,39].

This study's main conclusion is that endogenous GH cannot be acutely decreased by a single cabergoline application during pegvisomant treatment in a cohort of therapy resistant acromegalic patients. But in 4 patients a decline >30% was observed, which might indicate dopamine responsiveness in these patients. Moreover, cabergoline improves glucose sensitivity. Long term data of combined treatment with pegvisomant and dopamine agonists are necessary to evaluate whether co-treatment can effectively reduce pegvisomant induced increases of endogenous GH, which would greatly improve disease management.

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