GH activity and markers of inflammation: a crossover study in healthy volunteers treated with GH and a GH receptor antagonist

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Abstract

Introduction: The GH/IGF1 axis may modulate inflammatory processes. However, the relationship seems complicated as both pro- and anti-inflammatory effects have been demonstrated.

Methods/design: Twelve healthy volunteers (mean age 36, range 27–49 years) were treated in random order with increasing doses of GH for 3 weeks (first week 0.01 mg/kg per day, second week 0.02 mg/kg per day, and third week 0.03 mg/kg per day) or a GH receptor antagonist (pegvisomant; first week 10 mg/day and last two weeks 15 mg/day), separated by 8 weeks of washout. Circulating levels of the pro-inflammatory cytokines tumor necrosis factor α (TNFα), interleukin 6 (IL6), and IL1β (IL1B) and the acute phase proteins (APPs) C-reactive protein (CRP), haptoglobin, orosomucoid, YKL40 (CHI3L1), and fibrinogen were measured.

Results: During GH treatment, IGF1 (median 131 (Inter-quartile range (IQR) 112–166) vs 390 (322–524) μg/l, P=0.002) increased together with TNFα (0.87 (0.74–1.48) vs 1.27 (0.80–1.69) ng/l, P=0.003), IL6 (1.00 (0.83–1.55) vs 1.35 (0.80–4.28) ng/l, P=0.045), and fibrinogen (9.2 (8.8–9.6) vs 11.1 (9.4–12.4) μM, P=0.002). By contrast, orosomucoid decreased (18.0 (15.5–24.3) vs 15.0 (15.0–17.0) μM, P=0.018). CRP, YKL40, and haptoglobin were unchanged. During pegvisomant treatment, IGF1 decreased (139 (117–171) vs 91 (78–114) ng/ml, P=0.005). Orosomucoid (21.0 (16.3–23.8) vs 22.0 (17.0–29.3) μM, P=0.036) and CRP (1.00 (0.62–1.77) vs 1.43 (0.71–3.29) mg/l, P=0.074) increased without an increase in pro-inflammatory cytokines.

Conclusions: GH/IGF1 action appears to modulate the initial stage of the inflammatory response as well as downstream processes elucidated by levels of APPs. The data suggest a complicated relationship not allowing any simple conclusions as to whether GH/IGF1 actions have mainly pro- or anti-inflammatory effects in vivo.

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Introduction

An increasing amount of data has supported a connection between the innate immune system and the activity of the GH/insulin-like growth factor 1 (IGF1) axis (1, 2, 3, 4). The vast majority of clinical and experimental studies have focused on stages with increased inflammation where it seems that chronic inflammation suppresses the GH/IGF1 axis (2, 5, 6, 7, 8, 9). In addition, more recent observations have demonstrated that the relationship may be bidirectional, with GH/IGF1 activity influencing inflammatory processes (3, 10, 11). However, the association seems complicated as data obtained from in vivo and in vitro studies have been supporting pro-inflammatory (3, 12, 13) as well as anti-inflammatory effects of GH and IGF1 (3, 13, 14, 15).

The innate immune system comprises those cells and mechanisms that defend the host from infective and other inflammatory processes in a nonspecific manner. Pro-inflammatory cytokines produced by macrophages and other leukocytes are key factors in the innate immune response (16, 17, 18). The pro-inflammatory cytokines stimulate the secretion of a variety of acute phase proteins (APPs) participating in the inflammatory cascade (17). APPs are primarily secreted by hepatocytes and divided into two groups: class 1 APPs mainly induced by IL1β (IL1B) or a combination of IL1β and IL6. This class includes, e.g. CRP, haptoglobin, and orosomucoid. Class 2 APPs include fibrinogen and α2-macroglobulin, and mainly respond to IL6 but not IL1β (19, 20). Another important pro-inflammatory cytokine is tumor necrosis factor α (TNFα, TNFA)).
In recent years, it has become evident that the innate immune system may also be activated in chronic nonclassical inflammatory diseases, resulting in a subsequent low-grade chronic inflammation (21). The pathophysiological consequence is debated but chronic inflammation might be a pathogenetic factor in aging processes and specifically in the development of cardiovascular disease (CVD) (21, 22).

In this study, we examined the possible effects on various inflammatory markers of 3 weeks of GH excess and 3 weeks of GH inhibition in healthy volunteers. Activity in the immune system was evaluated by leukocyte numbers, circulating levels of pro-inflammatory cytokines, different hepatic class I and class II APPs, and serum YKL40 (CHI3L1), which is a novel APP secreted by fibroblasts and chondrocytes but not by hepatocytes (23). The purpose was to investigate short-term in vivo effects of high and low GH/IGF1 activity on inflammatory processes. The hypothesis based on our previous observations in acromegalic and GH-deficient patients was that GH and IGF1 exert anti-inflammatory effects (15).

### Subjects and methods

#### Study design

This was a randomized crossover study. Participants were treated for 3 weeks, in random order, with increasing doses of s.c. injections of GH (genotropin, mini-quick; Pfizer, first week 0.01 mg/kg per day, second week 0.02 mg/kg per day, third week 0.03 mg/kg per day) or with s.c. injections of a GH receptor antagonist (pegvisomant; Pfizer; first week 10 mg/day, last two weeks 15 mg/day). During GH treatment, the aim was to maintain the IGF1 levels within the acromegalic range. The dose was chosen based on the experiences from previous experimental studies (24, 25, 26). During GH receptor blockade we aimed to mimic severe GHD. The 15 mg/day dose was chosen based on the experiences with treatment of acromegalic patients with severe GH hypersecretion (27). The two treatment regimens were separated by an 8-week washout period. Half of the participants had GH as the initial treatment, whereas the other half were initiated with pegvisomant treatment. Before administration of GH/pegvisomant, participants were thoroughly instructed by a specialized nurse. The study medication was administrated at 2300 h.

The study consisted of ten visits including a screening visit and a follow-up visit 8 weeks after the latest injection. During the two treatment periods, patients were seen once every week, ~8 h after injection of medicine. At each visit, blood pressure, pulse, and weight were measured, injection sites were inspected, and fasting blood samples were collected. A physical examination was performed at the screening visit, before the two treatment periods and at follow-up. Safety parameters included plasma glucose, serum potassium, sodium, and creatinine, which were all measured at each visit. At screening and during pegvisomant treatment, measurement of hepatic transaminase (ASAT) was included. Additional serum and plasma samples were drawn and stored at −80 °C for later measurements of circulating levels of GH, pegvisomant, IGF1, leukocytes, TNFα, interleukin 6 (IL6), IL1β, CRP, haptoglobin, orosomucoid, YKL40, and fibrinogen. Serum GH, pegvisomant, and IGF1 were measured at each visit, whereas markers of inflammation were determined before and after the 3 weeks of treatment with GH and pegvisomant respectively.

#### Study population

The study population was recruited through a Danish internet-based advertising bureau specialized in recruiting participants for medical research. The inclusion criterion was age between 22 and 65 years. Exclusion criteria were chronic disease, body mass index (BMI) above 30 kg/m², daily intake of prescribed medication (except contraceptives), previous cancer disease, drug or alcohol abuse, pregnancy, or nursing. Furthermore, participants should have a normal physical examination at the screening visit, blood pressure below 140/90 mmHg, and levels of biochemical safety parameters within normal range.

The study population consisted of 12 healthy volunteers (nine males and three females) with a mean age of 36 (range 27–49) years, height 179 (IQR 172–190) cm, weight 80.7 (71.6–93.8) kg, and BMI 24.5 (23.2–27.0) kg/m². None of the females used oral contraceptives. One participant (female, age 37 years) decided to discontinue the study after the first 3 weeks of GH treatment due to personal reasons. Based on the serum levels of pegvisomant and IGF1, it was obvious that another participant (female, age 27 years) failed to inject pegvisomant on a regular basis and therefore her data were not included in the statistical analyses concerning pegvisomant treatment (serum pegvisomant was undetectable after 1 and 2 weeks of treatment and only 938 ng/ml after 3 weeks). Thus, during GH stimulation, we had complete data for all the 12 individuals, whereas we had complete data for ten individuals during GH receptor blockade.

#### Biochemical analyses

Serum IGF1 was measured by a solid phase ELISA (R&D Systems, Minneapolis, MN, USA) with a measuring range of 2.6–600 μg/l. The intra- and interassay coefficients of variation (CV) for medium levels were 3 and 7 respectively (28).

Serum GH was measured by a commercial time-resolved immunofluorometric assay (TR-IFMA) from Perkin Elmer Life Sciences (Dellfa, Turku, Finland) following validated modifications as described previously (29). Normally, the assay is a one-step assay.
in which serum and a europium-labeled GH detection antibody are incubated in microtiter wells precoated with another GH antibody. In contrast to the detection antibody, the coating antibody does not recognize pegvisomant, and accordingly, it is possible to measure GH in the presence of pegvisomant while using separate incubation steps for serum samples and the detection antibody. Intra-assay and interassay CV are not affected by the modification and are as stated by the manufacturer (29).

Serum pegvisomant was measured by an in-house RIA using diluted serum samples, which had been depleted of endogenous GH following pre-incubation in the microtiter wells from the Delfia GH TR-IFMA. Intra-assay CV ranged from 3 to 8%, whereas the interassay CV was 6% (29).

The following measurements were done: serum IL-6 levels by ELISA (highly sensitive; R&D Systems), lower detection limit 0.10 ng/l, and intra- and interassay CV were 8.7 and 15.1% respectively; serum TNFα by ELISA (highly sensitive; R&D Systems), lower detection limit 0.20 ng/l, and intra- and interassay CV (mean level 1.83 ng/l) 8.5 and 10.6% respectively (information provided by the manufacturer); plasma IL-1β by ELISA (highly sensitive; R&D Systems), lower detection limit 0.102 ng/l, and intra- and interassay CV (mean level 0.28 ng/l) 10.2 and 10.4% respectively (information provided by the manufacturer); serum YKL40 levels by a high-sensitivity turbidimetry assay (Dako (Glostrup, Denmark) on a Konelab 60 analyzer), lower detection limit 20 µg/l, and intra- and interassay CV 5.8 and 6.0% respectively; serum CRP by a high-sensitivity turbidimetry assay (Dako (Glostrup, Denmark) on a Konelab 60 analyzer), lower detection limit 0.20 mg/l, and interassay CV (mean level 1.7 mg/l) 3% (30); plasma haptoglobin by a method based on immunoprecipitation enhanced by polyethylene glycol (Thermo Scientific (Boston, MA, USA) on a Konelab analyzer/T Series), measuring range 1–35 µmol/l, and intra- and interassay CV (mean level 6.9 µmol/l) 1.1 and 2.2% respectively (information provided by the manufacturer); and plasma orosomucoid by immunoturbidimetric (Thermo Scientific on a Konelab analyzer/T Series), measuring range 3.8–69.8 µmol/l, and intra- and interassay CV (mean level 23 µmol/l) 1.6 and 1.6% respectively (information provided by the manufacturer). Fibrinogen was measured in human citrated plasma using a coagulometric method (PT-Fibrinogen HS PLUS; Instrumentation Laboratory on an ACL TOP analyzer), measuring range 2.4–29.4 µmol/l, and intra- and interassay CV (mean level 8.1 µmol/l) 2.0 and 3.2% respectively (information provided by the manufacturer).

Statistical analyses

Changes in the different inflammatory markers, plasma glucose, and body weight were evaluated by paired nonparametric statistical analyses (Wilcoxon’s rank sum test). For each variable, three analyses were conducted: pre-GH treatment vs 3 weeks of GH treatment, pre-pegvisomant vs 3 weeks of pegvisomant treatment, and 3 weeks of GH vs 3 weeks of pegvisomant treatment. Markers reflecting GH activity were measured every week and analyzed by Friedman repeated measures analyses. Data are expressed as mean ± s.d. for normally distributed variables and median (IQR) for non-normally distributed variables.

Ethics

The study was approved by the Local Committee of Ethics in Copenhagen (protocol ID HC-2009-049) and was performed in accordance with Good Clinical Practice rules. The study was registered at www.clinicaltrials.gov protocol ID NCT00969644.

Results

There was a significant increase in serum IGF1 following 3 weeks of GH treatment (median 130 (IQR 112–166) at baseline vs 390 (322–524) µg/l, P < 0.001, Fig. 1B) and a decrease during GH receptor blockage (139 (117–171) vs 91 (78–114) µg/l, P < 0.001, Fig. 1D). After 3 weeks of GH treatment, IGF1 levels were comparable to levels measured in untreated acromegalic patients using the same IGF1 assay (31). IGF1 levels after 3 weeks of GH receptor blockage were somewhat higher than in our last series of untreated GH-deficient patients (91 (78–114) vs 60 (43–84) µg/l) (32). Serum GH showed a stepwise increase parallel to the escalating doses of injected GH (Fig. 1A), whereas pegvisomant treatment was accompanied by the expected compensatory increase in endogenous GH levels (Fig. 1C). Serum pegvisomant increased from 2067 (958–2800) µg/l after 1 week to

Figure 1 Changes in levels of GH, IGF1, and pegvisomant during GH treatment (panels A and B) and pegvisomant treatment (panels C, D and E). All variables were measured before and after 1, 2, and 3 weeks of GH and pegvisomant treatment respectively. Blood samples were taken 8 h after the latest injection of study medication.
Markers of inflammation: GH treatment

During the 3 weeks of GH treatment, there was an increase in the levels of IL6 (1.00 (0.83–1.55) vs 1.35 (0.89–4.28) ng/l, P = 0.045) and TNFα (0.87 (0.74–1.48) vs 1.27 (0.80–1.69) ng/l, P = 0.003) and a parallel increase in levels of fibrinogen (9.2 (8.8–9.6) vs 11.1 (9.4–12.0) μmol/l, P = 0.002; Table 1, Fig. 2A, B and G). By contrast, levels of orosomucoid showed a decrease (18.0 (15.5–24.3) vs 15.0 (15.0–17.0) μmol/l, P = 0.018; Table 1, Fig. 2D). Serum CRP, haptoglobin, and YKL40 were unchanged (Table 1 and Fig. 2C, E and F). Adjusted for multiple comparisons using the Bonferroni correction, none of the results were statistically significant.

Markers of inflammation: pegvisomant treatment

During pegvisomant treatment, levels of IL6 and TNFα decreased numerically, but the changes were statistically nonsignificant (Table 1 and Fig. 2A and B). Among the APPs, levels of orosomucoid increased (21.0 (16.3–23.8) vs 22.0 (17.0–29.3) μmol/l, P = 0.036; Fig. 2D) and levels of CRP showed a trend toward an increase (1.00 (0.62–1.77) vs 1.43 (0.71–3.29) mg/l, P = 0.074; Table 1 and Fig. 2E). Circulating levels of the other APPs remained unchanged (Table 1 and Fig. 2C) and orosomucoid (P = 0.021) and fibrinogen (P = 0.014) remained statistically significant.

Markers of inflammation: GH treatment vs pegvisomant treatment

Significantly higher levels of TNFα were found during GH treatment compared with pegvisomant treatment (P = 0.047; Table 1 and Fig. 2A). By contrast, levels of CRP (P = 0.037; Table 1 and Fig. 2C) and orosomucoid (P = 0.005; Table 1 and Fig. 2D) were lower during GH treatment compared with GH receptor blockage with pegvisomant. The opposite was observed for fibrinogen (P = 0.005), which was found to be higher during GH treatment (Table 1 and Fig. 2G). After Bonferroni correction, changes in levels of orosomucoid (P = 0.035) and fibrinogen (P = 0.035) remained statistically significant.
Discussion

This study demonstrates that in vivo, 3 weeks of GH treatment or GH inhibition exerts complex effects on the innate immune system in normal healthy individuals. During GH treatment, we observed an increase in levels of pro-inflammatory cytokines with subsequent equivocal changes in levels of downstream APPs: plasma fibrinogen increased, plasma orosomucoid decreased, and levels of YKL40, CRP, and haptoglobin.
were unchanged. Conversely, during GH inhibition, levels of orosomucoid and CRP increased despite unchanged levels of TNFα and IL6. Taken together, GH/IGF1 appeared to stimulate the initial phase of the innate immune response as evaluated by levels of pro-inflammatory cytokines, whereas the influence on levels of APPs was inconsistent.

The increase in serum TNFα and IL6 induced by GH treatment is in accordance with a short-term study on children with GH deficiency where increased levels of TNFα and IL6 were observed 6 h after a single s.c. GH injection (12). A direct stimulating effect of GH is further supported by in vitro studies where both GH and IGF1 administrations seem to increase TNFα and IL6 secretion from activated lymphocytes (13, 33). It cannot be excluded that the increase in blood glucose during GH treatment (Table 1) might also have had a direct stimulating effect on secretion of TNFα and IL6 as observed in diabetic patients postprandially (34). However, compared with observations in diabetes, the increase in blood glucose in our study was very small and therefore unlikely to play a major role for cytokine secretion (34).

It is important to emphasize that the direct stimulating effects of GH/IGF1 on pro-inflammatory cytokines are in contrast to what has been observed in patients with chronic GH disturbances. In untreated GH-deficient patients, unchanged (15) or increased levels of IL6 and TNFα have been reported (35, 36), and subsequent GH replacement therapy decreased rather than increased levels of TNFα and IL6 (36, 37). In untreated acromegalic patients, a recent study demonstrated increased levels of TNFα (38), but two other studies showed that in active acromegaly, the secretion of IL6 was normal, despite chronically elevated levels of GH and IGF1 (14, 15). One explanation is that GH/IGF1-dependent changes in body fat may outweigh the direct effects of GH/IGF1 on IL6. Thus, in patients with untreated GHD, the presence of increased body fat may lead to a subsequent hypersecretion of pro-inflammatory cytokines, whereas the opposite may be the case in untreated acromegaly where reduced body fat has been reported (39).

As an interesting observation from the current study, GH/IGF1 action seemed to interfere with the relationship between pro-inflammatory cytokines and the corresponding changes in the levels of APPs. Levels of the class II APP fibrinogen changed in parallel with changes in levels of pro-inflammatory cytokines, as one would expect (17, 40). By contrast, the secretion of the class I APPs was inhibited by high GH/IGF1 activity, with unchanged or even reduced levels during GH treatment, despite increased levels of pro-inflammatory cytokines. The opposite was found during GH receptor blockage, where levels of orosomucoid and CRP increased from baseline values without a concomitant increase in levels of pro-inflammatory cytokines. When comparing GH treatment and GH receptor blockage, there was a significant increase in levels of TNFα and a decrease in levels of orosomucoid and CRP.

We do not have any solid explanation for the somewhat paradoxical changes in markers of inflammation during manipulation of the GH/IGF1 axis, with levels of pro-inflammatory cytokines and class I APPs going in opposite directions, yet some hypotheses may be suggested. As one possibility, GH and/or IGF1 may induce a state of resistance to the action of the pro-inflammatory cytokines. This hypothesis is supported by one in vitro study that showed that GH induces resistance to IL6 and IL1β stimulations (41). Moreover, a study on mice demonstrated that IGF1 administrated into the lateral ventricles of the brain completely blocked sickness behavior induced by TNFα injections (42). It is well documented that inflammation induces resistance to GH and IGF1 action with several studies indicating that elevated levels of IL6, TNFα, and IL1β per se are involved in these processes (9, 43, 44). Thus, there might be a reciprocal relationship between GH/IGF1 activity and pro-inflammatory cytokine action. GH and IL6 receptors belong to the class I cytokine receptors, which show structural similarities and share intracellular regulatory pathways, thereby implying the possibility of various intracellular interactions between IL6, GH, and their receptors (45, 46). For IGF1, similar intracellular cross talks have been suggested primarily linking IGF1 and TNFα activity (4, 8, 42).

As another possibility, the observed changes in APPs may be secondary to GH/IGF1-dependent changes in other important pro- or anti-inflammatory cytokines. For instance, a recent in vitro study showed that IGF1 stimulated the secretion of TNFα and IL6 but inhibited the secretion of IL1β (13). Increased levels of TNFα and IL6 and decreased levels of IL1β are compatible with reduced or unchanged levels of class I APPs (costimulated by IL1β and IL6) and increased levels of class II APPs, which are primarily stimulated by IL6 and not by IL1β. Circulating levels of IL1β are very low during noninflammatory conditions, and even with a highly sensitive assay, we were unable to detect plasma IL1β. Therefore, this hypothesis could unfortunately not be further elucidated.

The results on APPs are supported by clinical studies on patients with GH disturbances. Reduced levels of CRP have been demonstrated several times in active acromegaly with normalization after control of the disease (14, 15, 47). Moreover, one study in active acromegaly reported increased levels of fibrinogen together with reduced CPR, in agreement with our observations (47). In untreated GHD, increased baseline CRP has been observed with subsequent reductions during GH replacement therapy (15, 48, 49). However, in patients with long-term GH disturbances, changes in levels of APPs may not be solely dependent on direct effects of GH and IGF1. Secondary changes caused by GH/IGF1 actions well documented influence on body
composition may also contribute (39, 50, 51). One previous experimental study has investigated short-term high-dose GH treatment in healthy volunteers. In that study, no significant changes in levels of haptoglobin or CRP were reported (52).

The relationship between chronic inflammation and CVD has been intensively studied during recent years, and at present, it seems beyond doubt that an association between inflammation and atherosclerosis exists (22). Furthermore, longitudinal population-based studies, as well as studies on patients with chronic inflammatory diseases like rheumatoid arthritis, point to the possibility that inflammation may be causally involved in the pathogenesis of atherosclerosis (53, 54, 55). CRP per se has been proposed as a causal factor, but a recent study on individuals with genetically isolated increased CRP did not find evidence of this hypothesis (56). Thus, it is unclear which components of the inflammatory cascade are the major pro-atherosclerotic factors. In this perspective, it is important to emphasize that our data suggest that GH/IGF1 action may interfere with the innate immune system in a direct and unique way, where it is not possible to draw simple conclusions as to whether GH/IGF1 action exerts pro- or anti-inflammatory effects. Consequently, we speculate that it may not be appropriate to extrapolate results on inflammatory risk factors from populations with an intact GH axis to patients with GH disturbances. As one example, high CRP levels in GHD and low levels in intact GH axis to patients with GH disturbances. As one example, high CRP levels in GHD and low levels in intact GH/IGF1 action may interfere with the innate immune system (57). Survival studies on acromegaly have not shown increased mortality related to infections (58). However, exogenous GH therapy in critically ill patients led to increased mortality primarily caused by septic shock and multiorgan failure (59). Thus, an intact GH/IGF1 axis may be important to maintain an intact immune function.

This is the first in vivo study on humans investigating the influence of experimental blockade of GH action on inflammation. The daily dose of pegvisomant and the measured circulating levels were in the range that has been reported in sufficiently treated acromegalic patients with severe hypersecretion of GH (27). Thus, although serum IGF1 only decreased by ~40%, the high serum levels of pegvisomant support a sufficient blockage of the GH receptors. In this perspective, one should have in mind that there are numerous factors, besides GH, contributing to IGF1 formation as illustrated by the fact that even severely affected GH-deficient patients often have IGF1 values within the normal range (60, 61).

In conclusion, the present in vivo study on humans further supports a regulatory role of GH and IGF1 on the innate immune system. Overall, the data are compatible with a complicated relationship where GH may modulate the initial stage elucidated by levels of pro-inflammatory cytokines as well as downstream processes as judged by levels of APPs.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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