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Growth Hormone & IGF Research 15 (2005) 300–303
www.elsevier.com/locate/ghir

Changes in insulin sensitivity induced by short-term growth hormone (GH) and insulin-like growth factor I (IGF-I) treatment in GH-deficient adults are not associated with changes in adiponectin levels

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Received 20 December 2004; revised 25 May 2005; accepted 1 June 2005
Available online 27 July 2005

Abstract

To test potential effects of altered insulin sensitivity on circulating adiponectin levels, we studied patients with GH deficiency (GHD) undergoing high dose GH and IGF-I treatment in a well-defined short-term setting. This design allowed to exclude confounding effects of GH and IGF-I treatment on body composition. Six patients (three women and three men) with acquired GHD were treated in a randomised cross-over trial with GH (subcutaneous injections of GH 0.03 IU/kg/daily) or IGF-I (continuous subcutaneous infusion of 5 μg/kg/h recombinant IGF-I) for 5 days. Median age of patients was 60 (range 25–72) years, BMI 24.7 (20.7–30.7) kg/m^2, and baseline IGF-I concentration 60 (30–83) μg/L. HOMA scores (to assess insulin sensitivity) at baseline were 0.8 (0.3–11.7) and adiponectin concentrations were 7.0 (2.5–14.8) mg/L. HOMA scores increased rapidly and significantly up to a maximum of 2.7-fold (from baseline) at day 5 of GH treatment and returned promptly to baseline when GH was stopped, while adiponectin serum levels remained within the baseline range throughout the study period. HOMA scores dropped to a nadir of 0.66 from baseline at day 2 of IGF-I treatment whereas adiponectin levels remained within the baseline range. These data suggest that changes in insulin sensitivity (induced by high dose and short-term GH and IGF-I treatment) in patients with GHD are not associated with changes in adiponectin levels.

Keywords: Growth hormone; Adiponectin; Insulin sensitivity; IGF-I

1. Introduction

Circulating adiponectin levels have been shown to be positively correlated with insulin sensitivity and negatively with visceral fat. Accordingly, decreased adiponectin levels have been found in obese individuals and in patients with type 2 diabetes [1,2]. In patients with type 2 diabetes undergoing treatment with thiazolidinedione drugs, a close correlation of improved insulin sensitivity, decreased hepatic fat content, and increasing adiponectin levels has been described [3].

In patients with GH excess and deficiency, the relationship between circulating adiponectin and insulin sensitivity is less clear [4]. It is well known that insulin sensitivity is decreased in patients with GH excess and deficiency as well. However, whereas visceral fat is increased in patient with GH deficiency it is decreased in patients with acromegaly. Interestingly, GH replacement therapy for several months in patients with GH deficiency did not change circulating adiponectin levels [5,6]. In contrast, circulating adiponectin levels increased

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doi:10.1016/j.ghir.2005.06.012

several months after pituitary surgery in patients with acromegaly [7,8]. However, the relationship between circulating adiponectin and insulin sensitivity remains unclear since changes in body composition and insulin sensitivity may counteract each others effects in these studies with follow-up periods of several months.

High dose short-term GH treatment reduces while IGF-I treatment increases insulin sensitivity [9,10]. To test the relationship between insulin sensitivity and adiponectin levels in patients with GH deficiency (GHD), we studied patients with GHD undergoing high dose GH and IGF-I treatment in a well-defined short-term setting, i.e. before changes in body composition come into play.

2. Subjects and methods

2.1. Subjects

In a previously published randomised cross-over trial, we treated eight patients with acquired GHD with GH and IGF-I [11]. Two patients with diabetes were excluded from the current analysis: one patient had type 2 diabetes and was treated with a sulfonylurea; the other patient developed blood glucose concentrations in the diabetic range during the GH treatment. Median (range) age of the six remaining patients (three women and three men) was 60 (25–72) years, BMI 24.7 (20.7–30.7) kg/m^2. All patients had GHD deficiency due to pituitary tumours for more than 2 years. Baseline IGF-I concentrations were 60 (30–83) μg/L. None of the patients had been treated with GH prior to the study and replacement therapy with other hormones remained unchanged during the study period.

2.2. Ethical considerations

The study protocol had been approved by the Ethics committee of the University Hospital of Zurich. Written informed consent was obtained from all patients.

2.3. Study protocol

Patients had been treated in a randomised cross-over trial with GH and IGF-I. Patients were treated for 5 days with subcutaneous injections of GH (0.03 IU/kg/daily at 20.00 h) or a continuous subcutaneous infusion of 5 μg/kg/h recombinant IGF-I. The wash-out period between the two treatment periods lasted 10 weeks. We determined insulin sensitivity (as assessed by HOMA) and adiponectin levels before, during, and after the treatment with GH- and IGF-I. All blood samples had been collected after a 10-h overnight fast at 08.00 h. Patients had been advised not to change their diet or life-style during the study.

2.4. Biochemical assays

Fasting plasma glucose levels were determined immediately by the glucose oxidase technique (Beckman Analyzer; Beckman, Fullerton, CA). Serum insulin levels were determined in frozen samples a few weeks after the study had been completed by a two-site enzyme-linked immunosorbent assay (DAKO Ltd., Cambridgeshire, UK). Reference interval (95% confidence interval) in healthy individuals provided by the manufacturer was 11–86 pmol/L, the lower limit of detection 3 pmol/L. Insulin sensitivity was estimated using homeostasis model assessment (HOMA), mainly reflecting hepatic insulin sensitivity [12]. The samples (stored for 9 years) were used more recently for the analysis of adiponectin serum levels by a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) validated for serum and plasma (R&D Systems Europe, Abingdon, UK). The intra-assay coefficient of variation was 4.8%, the inter-assay coefficient 7.3%, and the reference range 0.9–21.4 mg/L.

For the determination of IGF-I, IGF binding proteins were removed by Sep-Pak® chromatography

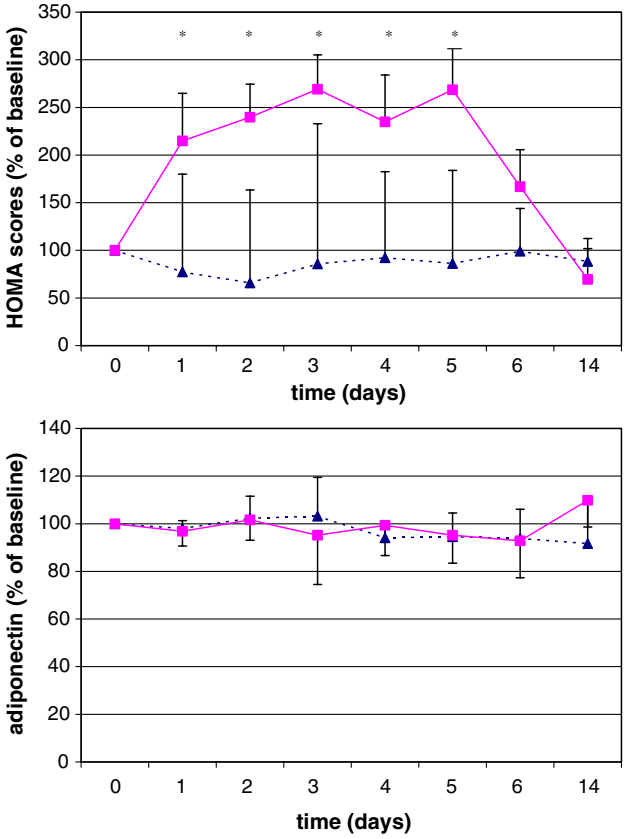

Fig. 1. HOMA scores (upper panel) and adiponectin levels (lower panel) compared to baseline values in six patients with GHD treated with GH (squares, solid line) and IGF-I (triangles, broken line) for 5 days (from day 1 to day 5). Data are shown as mean ± SD. $^*p < 0.05$ from baseline by Wilcoxon signed rank test.