Effects of a Combination of Recombinant Human Growth Hormone with Metformin on Glucose Metabolism and Body Composition in Patients with Metabolic Syndrome

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Abstract

Abdominal obesity and insulin resistance are central findings in metabolic syndrome. Since treatment with recombinant human growth hormone (rhGH) can reduce body fat mass in patients with organic GH deficiency, rhGH therapy may also have favourable effects on patients with metabolic syndrome. However, due to the highly increased risk for type 2 diabetes in these patients, strategies are needed to reduce the antagonistic effect of rhGH against insulin. We conducted a 18-month randomised, double-blind, placebo-controlled study to assess the effect of rhGH in combination with metformin (Met) in patients with metabolic syndrome. 25 obese men (55 ± 6 years, BMI 33.4 ± 2.9 kg/m^2) with mildly elevated fasting plasma glucose (FPG) levels at screening (6.1 – 8.0 mmol/l) were included. All patients received metformin (850 mg twice daily) either alone or in combination with rhGH (daily dose 9.5 µg/kg body weight). An oGTT was performed at baseline, after 6 weeks, and after 3, 6, 12, and 18 months of therapy. Glucose disposal rate (GDR) was measured by euglycemic hyperinsulinemic clamp at 0 and 18 months and body composition was measured by DEXA every 6 months. In the Met + GH group, IGF-I increased from 146 ± 56 µg/l to 373 ± 111 µg/l (mean ± SD) after 3 months and remained stable after that. BMI did not change significantly in either group during the study. Total body fat decreased by –4.3 ± 5.4 kg in the Met + GH group and by –2.7 ± 2.9 kg in the Met + Placebo group (differences between the two groups: p = n. s.). Waist circumference decreased in both groups (Met + GH: 118 ± 8 cm at baseline, 112 ± 10 cm after 18 months; Met + Placebo: 114 ± 7 cm *vs.* 109 ± 8 cm; differences between the two groups: p = 0.096). In the Met + GH group, FPG increased significantly after 6 months (5.9 ± 0.7 *vs.* 6.7 ± 0.4 mmol/l; p = 0.005), but subsequently decreased to baseline levels (18 months: 5.8 ± 0.2 mmol/l). FPG remained stable in the Met + Placebo group until 12 months had elapsed, and then slightly decreased (baseline: 6.2 ± 0.3, 18 months: 5.5 ± 0.6 mmol/l, p = 0.02). No significant changes were seen in either group regarding glucose and insulin AUC during oGTT or HbA_{1c} levels. GDR at 18 months increased by 20 ± 39 % in Met + GH-group and decreased by –11 ± 25 % in the Met + Placebo group (differences between the two groups: p = 0.07). In conclusion, treatment of patients with metabolic syndrome and elevated FPG levels did not cause sustained negative effects on glucose metabolism or insulin sensitivity if given in combination with metformin. However, since our data did not show significant differences between the two treatment groups with respect to body composition or lipid metabolism, future studies including larger numbers of patients will have to clarify whether the positive effects of rhGH on cardiovascular risk factors that have been shown in patients with GH deficiency are also present in patients with metabolic syndrome, and are additive to the effects of metformin.

Key words
Growth hormone · Metformin · Metabolic syndrome

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Introduction

The association of cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipoproteinemia, and obesity has long been known, and has been termed "metabolic syndrome" [1]. There are striking similarities between metabolic syndrome and untreated growth-hormone (GH) deficiency due to pituitary or hypothalamic pathologies [2–4]. The most central findings in both these entities are abdominal obesity and insulin resistance [3,5–7]. These similarities indicate that reduced GH action may play a role in the pathogenesis of metabolic aberrations – not only in GH deficiency, but also in metabolic syndrome.

In fact, there is striking evidence of a neuroendocrine GH secretion regulation disturbance in obesity. As body weight increases, GH secretion becomes blunted with a decrease in the mass of GH secreted per burst, but without any major impact on secretory burst frequency [8]. Furthermore, IGF-I serum levels are inversely related to body fat GH percentage [8–11] – in particular, to the amount of visceral adipose tissue [12].

In patients with GH deficiency, the beneficial effects of replacement therapy with recombinant human GH (rhGH) on most of the clinical features of the adult GH deficiency syndrome are well-established [3,13,14]. These effects include body fat reduction, improvement in risk factors for cardiovascular disease, and normalisation of other metabolic alterations. Johannsson et al. [3] have recently provided preliminary evidence that the beneficial effects of rhGH therapy might also be achieved in abdominally obese patients without evidence of pituitary disease. In this placebo-controlled trial, treatment of viscerally obese males with rhGH over a period of 9 months resulted in a reduction of abdominal fat mass and an improvement in glucose and lipid metabolism. None of these patients had elevated fasting plasma glucose levels.

The use of rhGH in patients with central obesity, however, may be limited by an increase in insulin resistance, which is known to occur during the early course of rhGH therapy [15]. This may be of particular importance in metabolic syndrome patients characterised by a highly increased risk of developing type 2 diabetes.

Metformin, a biguanide antihyperglycemic agent, has established itself in the treatment of obesity in connection with type 2 diabetes [16]. Very recently, metformin treatment has also been shown to be effective in the prevention of type 2 diabetes in high-risk populations [17]. The aim of the present study was to investigate the effects of rhGH in combination with metformin on glucose metabolism and body fat in high-risk patients with metabolic syndrome.

Subjects and Methods

Patients

Twenty-five men (55 ± 6 y; range 46–66 y) recruited by advertisements in local newspapers were included in the study. All included patients had three or more criteria fulfilling the definition for metabolic syndrome according to the Third Report of the National Cholesterol Education Program [ATP III] [18] (1. Abdominal obesity: waist circumference > 102 cm in men; 2. Hypertriglyceridemia ≥ 1.695 mmol/l and/or HDL < 1.036 mmol/l in men; 4. high blood pressure ≥ 130/80 mm Hg; 5. high fasting glucose ≥ 6.1 mmol/l) based on the 1998 WHO definition [19]. Inclusion criteria were age between 35–70 years with a body mass index between 30–40 kg/m^2, fasting plasma glucose (FPG) between 6.1–8.0 mmol/l (impaired glucose tolerance/diabetes mellitus), and HbA_{1c} < 7.5 %. Three patients in the Metformin + GH group and two patients in the Metformin + Placebo group had diabetes mellitus at baseline (fasting plasma glucose > 7.0 mmol/l). Exclusion criteria were active smoking, current treatment with lipid-lowering or antidiabetic drugs or insulin, serum creatinine > 1.2 mg/day, previous cardiovascular or cerebrovascular events, reasons for elevated blood glucose concentrations other than type 2 diabetes, use of glucocorticoids during the last 3 months before study entry, hypertension with a blood pressure > 100 mm Hg diastolic or > 200 mm Hg systolic (with or without antihypertensive medication), chronic obstructive pulmonary disease, use of weight-reducing drugs such as orlistat or sibutramine during the last 3 months before study entry, elevated liver enzymes (SGOT (AST) > 100 U/l; SGPT (ALT) > 100 U/l), and any suspicion of malignant disease.

Study protocol

The design of the study was a 18-month, double-blind, placebo-controlled trial. Before study entry, informed consent was obtained from each patient. The patients were randomly assigned to one of two treatment groups – metformin and rhGH (Met + GH) or metformin and placebo (Met + Placebo). Treatment assignments were stratified according to BMI and HbA_{1c}. 12 patients were included in the Met + GH group and 13 patients in the Met + Placebo group. The study protocol was approved by the Ethics Committee at the University of Essen.

In both treatment groups, patients received metformin 850 mg twice daily (Glucophage®, Merck, Darmstadt, Germany) during the whole study period. In the Met + GH group, rhGH (Genotropin®, Pharmacia GmbH, Erlangen, Germany) was administered s.c. before bedtime at a daily dose of 9.5 μg/kg (0.20 IU/kg BW/week) after an initial 4-week dose-adjustment period. The rhGH chosen was equivalent to the dose used in the study from Johannsson et al. [3]. Patients in the Met + Placebo group were administered s.c. injections of placebo. The placebo vials contained the same vehicle as the rhGH vials, and both preparations were indistinguishable to the eye.

In both treatment groups, the daily dose was reduced by half where side effects occurred. Compliance was assessed by counting the returned empty vials.

Before study start, patients were screened by two determinations of FPG levels. All patients were hospitalised at baseline and after 18 months of treatment, and studied as outpatients during the study (after 6 weeks, 3 months, 6 months, and 12 months). Measurements of blood pressure, ECG, as well as physical and laboratory examinations were performed during all visits. Body weight was measured in the morning to the nearest 0.1 kg wearing indoor clothing, and body height was measured barefoot to the nearest 0.01 m. Waist circumference was meas-

ured in the standing position with a flexible plastic tape midway between the lower rib margin and the iliac crest. Systolic and diastolic blood pressures were measured after 10min of supine rest, repeated after 2 min to calculate mean value. Measurements of body composition were performed at baseline, and after 6, 12, and 18 months. A combined arginine-GHRH test was performed at baseline, and euglycemic hyperinsulinemic clamp tests were performed at baseline and after 18 months.

Body composition

Whole-body fat mass and lean body mass were assessed by dual energy X-ray absorptiometry (DEXA) (model DPX-L, Lunar Corporation, Madison, WI, USA).

Euglycemic hyperinsulinemic clamp

Euglycemic hyperinsulinemic clamp tests were performed based on the protocol of De Fronzo et al. [20,21]. Prior to the clamp study, all subjects consumed a diet containing at least 200 g of carbohydrate per day over 3 days. The studies were performed at 8 AM after a 12 h overnight fast. A polyethylene catheter was inserted into an antecubital vein for infusion of insulin and 20% dextrose. A second catheter was inserted into a hand vein and the hand was heated during the study to ensure arterialisation of venous blood. All blood samples for glucose and hormone analyses were drawn from the heated hand catheter. Insulin-mediated glucose disposal was determined using the euglycemic insulin clamp technique. Human insulin was administered as a continuous infusion (40 mU/m^2/min) for 180 min. Plasma glucose concentrations were measured every 5 min. Infusion of 20% dextrose began until 5min after the initiation of insulin infusion and was periodically adjusted to maintain the arterialised plasma glucose concentrations at 5.3 mmol/l. In-house reference values for glucose disposal rate (GDR) had already been evaluated in 30 healthy males, mean age 25 ± 2 years, BMI 23.0 ± 1.6 kg/m^2, GDR 10.2 ± 1.9 mg/kg/min (range 6.4 – 14.0).

Oral glucose tolerance test

After an overnight fast, subjects ingested a 75 g oral glucose load over a 3-min period. Blood samples for plasma glucose and serum insulin were obtained at baseline, and after 60 and 120 min.

Combined arginine plus GHRH (ARG-GHRH) test

GHRH (GHRH Ferring®, Kiel, Germany) at 1μg/kg BW was administered by an iv bolus followed by a 30 min infusion of arginine (30 g, Braun, Melsungen, Germany). In young, healthy, normal weight subjects, a GH peak > 9 μg/l was regarded as normal.

Assays

Serum GH levels were determined by a chemiluminescence immunometric assay (Nichols Institute Diagnostics GmbH, Bad Nauheim, Germany). The assay was calibrated against the WHO 1st international standard (80/505) for human GH. Intra- and interassay coefficients of variation (CVs) for a low point of the standard curve were 5.4% and 7.9%, respectively. Plasma IGF-I concentrations were measured by an immunoradiometric assay (Nichols Institute Diagnostics GmbH, Bad Nauheim, Germany). The assay was calibrated against the WHO 1st International Reference Reagent 87/518. Intra- and interassay CVs for low IGF-I concentrations were 2.4% and 5.2%, respectively. In our laboratory, the normal IGF-I ranges were 114 – 492 μg/l for adults aged 25 – 39 y, 90 – 360 μg/l for adults aged 40–54 y, and 71 – 290 μg/l for adults aged ≥ 55 y.

Plasma glucose was determined by the glucose oxidase method (glucose autoanalyzer, EBIO 6666, Eppendorf, Germany). Plasma insulin levels were assessed by radioimmunoassay (Biochem Immunosystems, Freiburg, Germany). HbA_{1c} was determined by DCA 2000 (Bayer, Leverkusen, Germany, upper limit 6.3%). Total testosterone was measured by an automated chemiluminescence immunoassay (ACS 180, Bayer Diagnostics, Fernwald, Germany).

Red blood cell counts, white blood cell counts, serum levels of sodium, potassium, creatinine, liver enzymes, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, lipoprotein (a) (Lp (a)), apolipoprotein A1, apolipoprotein B, fibrinogen, and prostate specific antigen were determined by routine methods.

Statistics

The data, if not otherwise noted, are represented as the mean ± standard deviation (SD). Comparisons between baseline values of the two groups were performed using the unpaired Wilcoxon/Mann/Whitney test (WMW). Absolute differences between time points were analysed per group using the paired Wilcoxon signed rank test (WSR). The areas under the curve of glucose and insulin were determined per unit time. Time courses were compared by repeated measure analysis of variance (RM ANOVA) for these AUC measures and for BMI and total body fat. Occurrence of side effects was compared by chi-square test (CHI). All p-values were given unadjusted and therefore interpreted exploratively. All tests were conducted at a two-sided significance level of 5%. Univariate analyses were performed with Graph.PadPrism (version 3.00 for Windows, GraphPad Software, San Diego, CA, USA) and RM ANOVA was performed using SAS V6.12.

Data from all 25 patients were included for analysis of parameter time courses by RM ANOVA.

Results

Patients' assignment to the two treatment groups was stratified according to BMI and HbA_{1c}. At baseline, the two groups did not differ significantly in terms of all other characteristics except systolic blood pressure (Met + GH: 136 ± 10 mm Hg *vs.* Met + Placebo: 126 ± 17 mm Hg; WMW p = 0.033) (Tables **1**, **2**).

Two patients in the Met + GH group and three patients in the Met + Placebo group received treatment for hypertension (Met + GH group: 12.5 mg/day hydrochlothiazide (12.5 mg/day) and 50 mg/day metoprolol, Met + Placebo group: amlodipine 10 mg/day; quinalapril 10 mg plus hydrochlorthiazide 12.5 mg/day and benazepril 10 mg/day). These medications were kept at a steady dose during the study period.

Side effects

Side effects were observed in 7/12 patients of the Met + GH group and in 8/13 patients of the Met + Placebo group (CHI p = 0.81). The side effects reported in the Met + GH group were arthralgia (5 patients) and peripheral oedema (2 patients). These side ef-

fects appeared during the first 6 weeks of treatment and subsided spontaneously in 3 patients. In 3 other patients, side effects subsided in response to dose reduction. Arthralgia persisted after dose reduction in one patient. In the Met + Placebo group, the side effects reported were headache (2 patients), transient paresthesia (2 patients), diarrhoea (2 patients), muscle stiffness (1 patient) and arthralgia (1 patient).

Dropout from the study occurred in 5 patients from the Met + GH group (4 due to non-compliance, 1 due to the requirement for additional antidiabetic drugs). In the Met + Placebo group, dropout occurred in 6 patients (5 due to non-compliance and 1 patient due to newly diagnosed plasmocytoma).

Overall, 22 patients were observed over a period of 6 months, 15 patients over 12 months and 14 patients (7 from the Met + GH group, 7 from the Met + Placebo group) completed the study (18 months).

ARG-GHRH test and IGF-I levels

At baseline, mean GH peaks in the ARG-GHRH test were reduced in both groups (Met + GH: 6.8 ± 3.7 ng/ml *vs.* Met + Placebo: 4.8 ± 2.9 ng/ml; differences between the two groups: WMW p = 0.15). Overall, 22/25 patients (88%) showed a maximum GH response < 9 µg/l.

The mean IGF-I levels at baseline were in the lower age-adjusted normal range in both groups (Met + GH: 173 ± 58 ng/ml *vs.* Met + Placebo: 144 ± 40 ng/ml; differences between the two groups: WMW p = 0.31). In the Met + GH group, IGF-I increased from 146 ± 56 µg/l to 373 ± 111 µg/l (WSR p < 0.001) after 3 months and remained stable thereafter (differences between the two groups, RM ANOVA p < 0.001) (Fig. **1**).

Body weight and body composition

Body weight (Met + GH: – 2.2 ± 5.7 kg *vs.* Met + Placebo: – 3.8 ± 4.2 kg; differences between the two groups: WMW p = 0.54) and BMI (Met + GH: – 1.16 ± 1.61 kg/m^2 *vs.* Met + Placebo: – 1.21 ± 1.37 kg/m^2; differences between the two groups: RM ANOVA p = 0.24) slightly decreased in both groups without reaching statistical significance (Fig. **2**). Mean total body fat significantly decreased by – 4.3 ± 5.5 kg (range: – 14.5 to 2.2 kg) in the Met + GH-group (WSR p = 0.04) and by – 2.7 ± 2.9 kg (range: – 6.7 to 0.4 kg) in the Met + Placebo group (WSR p = 0.007). The difference between the two groups, however, was not significant (RM ANOVA p = 0.91) (Fig. **2**). Lean body mass did not significantly change in both groups (Met + GH group: + 0.5 ± 3.8 kg; WSR p = 0.99; Met + Placebo: – 1.7 ± 2.7 kg; WSR p = 0.69; differences between the two groups: WMW p = 0.26). After 18 months, total muscle mass increased by 0.5 ± 3.7 kg in the Met + GH group (range – 4.6 to 3.7) and decreased by – 2.4 ± 2.9 in the Met + Placebo group (range – 5.7 to 2.2) (differences between the two groups WMW p = 0.16; Fig. **3**).

Waist circumference decreased during the study period in both groups (Met + GH: 118 ± 8 cm *vs.* 112 ± 10 cm; Met + Placebo: 114 ± 7 cm *vs.* 109 ± 8 cm; differences between the two groups: WMW p = 0.096) (Fig. **2**).

Glucose metabolism

According to the inclusion criteria, baseline FPG levels were slightly elevated in both groups (Met + GH: range 6.2 – 8.0 mmol/l; Met + Placebo: range 6.2 – 7.6 mmol/l; differences between the two groups: WMW p = 0.32) (Table **1**). During the first 6 months of treatment, FPG significantly increased in the Met + GH group (FPG: baseline 5.9 ± 0.7, 6 months 6.7 ± 0.4 mmol/l, WSR p = 0.005) (Fig. **3**). AUC of glucose levels during oGTT also slightly increased without reaching statistical significance (baseline 1005 ± 257 mmol/l/120 min, 6 months 1186 ±

Table **1** Baseline characteristics of 25 men with metabolic syndrome

	Metformin + GH group	*Metformin + Placebo group*
N	12	13
Mean age (yr)	54.3 ± 4.6	54.4 ± 5.7
BMI (kg/m^2)	33.7 ± 3.4	33.1 ± 2.5
Fasting plasma glucose (mmol/l)	6.7 ± 0.6	6.7 ± 0.5
Blood pressure		
systolic (mmHg)	136 ± 11	126 ± 16*
diastolic (mmHg)	88 ± 10	83 ± 11
Waist circumference (cm)	118 ± 8	114 ± 7

All values expressed means ± SD; *p = 0.033 (differences between the two groups by unpaired Wilcoxon/Mann/Whitney test)

Table **2** Lipid metabolism and fibrinogen of 25 men treated with Metformin + GH or Metformin + Placebo for 18 months

	Metformin + GH			*Metformin + Placebo*			*Normal Range*	
	Baseline	*18 months*	*P^a*	*Baseline*	*18 months*	*P^b*		*P^c*
Triglycerides (mmol/l)	1.9 ± 0.9	2.2 ± 1.0	0.56	1.8 ± 0.6	1.7 ± 0.5	0.38		0.31
Total cholesterol (mmol/l)	5.4 ± 1.0	5.1 ± 0.7	0.44	5.1 ± 0.9	5.6 ± 0.4	0.11		0.06
LDL cholesterol (mmol/l)	3.5 ± 0.9	3.1 ± 0.6	0.81	3.6 ± 0.6	3.4 ± 0.4	0.22		0.85
HDL cholesterol (mmol/l)	0.9 ± 0.1	1.2 ± 0.2	0.03	1.0 ± 0.1	1.4 ± 0.2	0.02		0.59
Lipoprotein (a) (g/l)	0.40 ± 0.45	0.93 ± 0.99	0.03	0.15 ± 0.08	0.48 ± 0.26	0.02	(0.0 – 3.0)	0.96
Apoliprotein A1 (g/l)	1.39 ± 0.12	1.56 ± 0.29	0.31	1.41 ± 0.11	1.58 ± 0.13	0.02	(1.15 – 1.90)	0.64
Apolipoprotein B (g/l)	1.07 ± 0.18	1.15 ± 0.17	0.44	1.04 ± 0.11	1.16 ± 0.11	0.02	(0.60 – 1.60)	0.67
Fibrinogen (g/l)	2.87 ± 0.39	3.13 ± 0.83	0.52	2.99 ± 0.29	3.03 ± 0.63	0.57	(1.6 – 4.5)	0.58

P^a denote the differences in the group treated with Metformin + GH by paired Wilcoxon signed rank test; P^b denote the differences in the group treated with Metformin + Placebo by paired Wilcoxon signed rank test; P^c denote the differences between the two groups by unpaired Wilcoxon/Mann/Whitney test

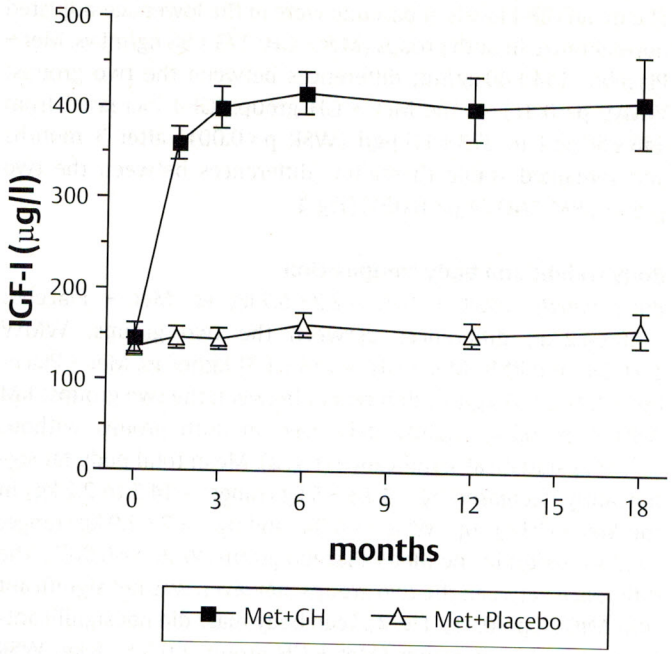

Fig. **1** Course of IGF-I levels (mean ± SEM) in the two groups of patients treated either with Metformin + GH (n = 12) or with Metformin + Placebo (n = 13). Analysis of the difference between the two groups by repeated measure analysis of variance (RM ANOVA) included the data from all 25 patients (p = 0.001).

203 mmol/l/120 min). The increases in FPG and AUC of glucose levels at 6 months returned to baseline levels during further treatment (after 18 months: FPG 5.8 ± 0.2 mmol/l; AUC glucose 1028 ± 202 mmol/l/120 min). In the Met + Placebo group, FPG remained stable until 12 months and decreased thereafter (baseline: 6.2 ± 0.3, 18 months: 5.5 ± 0.6 mmol/l, WSR p = 0.02). No significant differences were seen between the two groups with respect to the overall changes of FPG (RM ANOVA p = 0.32), the glucose AUC (RM ANOVA p = 0.52), the insulin AUC (RM ANOVA p = 0.51), and HbA_{1c} (Met + GH: 5.6 ± 0.4% at baseline to 5.6 ± 0.3% after 18 months, WSR p = 1.0; Met + Placebo: 6.0 ± 0.7 to 5.6 ± 0.4%, WSR p = 0.22; differences between the two groups: RM ANOVA p = 0.54).

At baseline, GDR did not differ significantly between the Met + GH and the Met + Placebo group (Met + GH: 3.9 ± 1.8 mg/kg/min; Met + Placebo: 5.7 ± 2.1 mg/kg/min; differences between the two groups: WMW p = 0.12). After 18 months of treatment, mean GDR increased in the Met + GH group (4.6 ± 2.4 mg/kg/min) and slightly decreased in the Met + Placebo group (4.8 ± 1.4 mg/kg/min). The difference between the two groups, however, did not reach statistical significance (WMW p = 0.07) (Fig. **4**).

Lipid metabolism and fibrinogen

At baseline, levels of triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol, Lp (a), apolipoprotein A1 and B were not statistically different between the two groups (Table **2**). In both groups, triglycerides, total cholesterol, LDL-cholesterol and fibrinogen levels did not change significantly during the 18-month period. HDL-cholesterol significantly increased in both groups (Table **2**). The apolipoprotein A1 and B increased significantly in the Met + Placebo group, but these parameters were unaffected

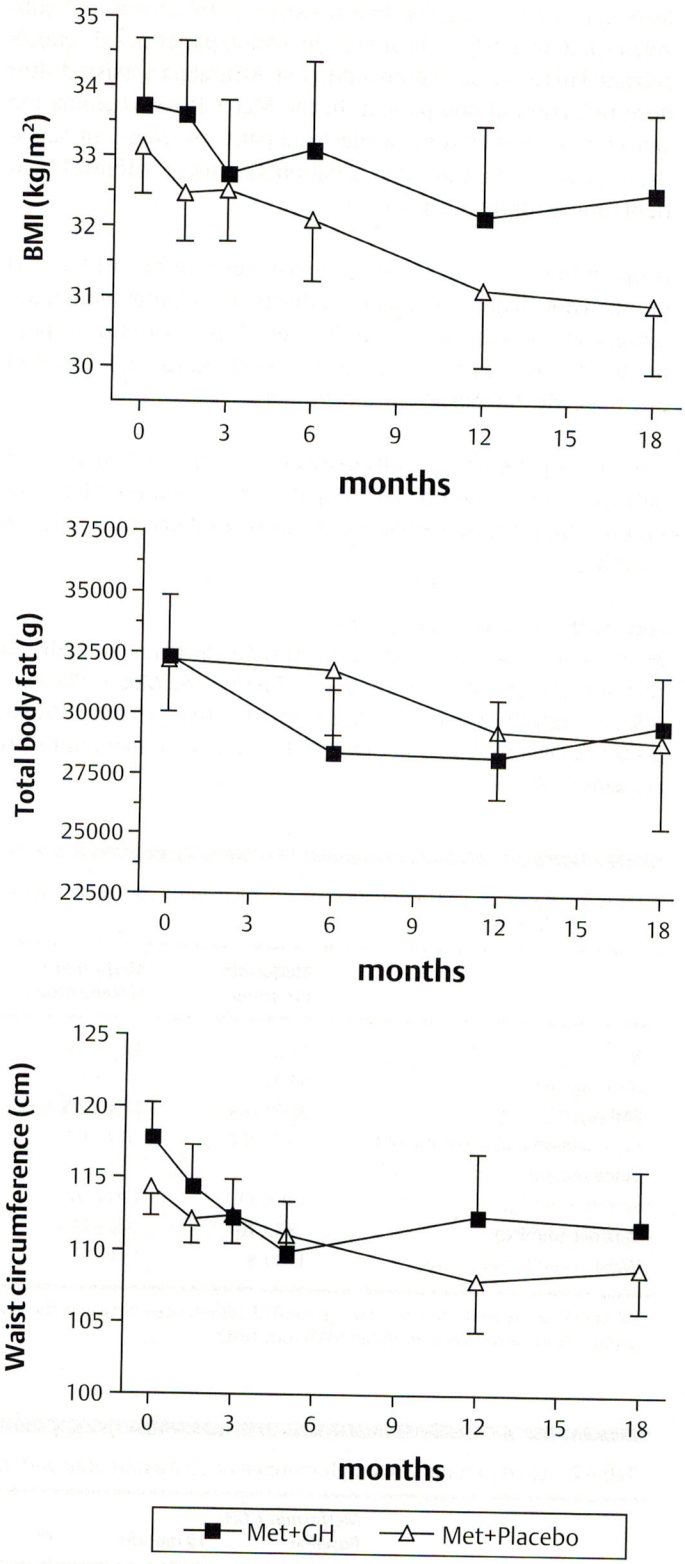

Fig. **2** Courses of BMI, total body fat, and waist circumference (mean ± SEM) in the two groups of patients treated either with Metformin + GH (n = 12) or with Metformin + Placebo (n = 13). Analysis of the differences between the two groups by repeated measure analysis of variance (RM ANOVA) included the data from all 25 patients (BMI: p = 0.24; total body fat: p = 0.91; waist circumference: p = 0.096).

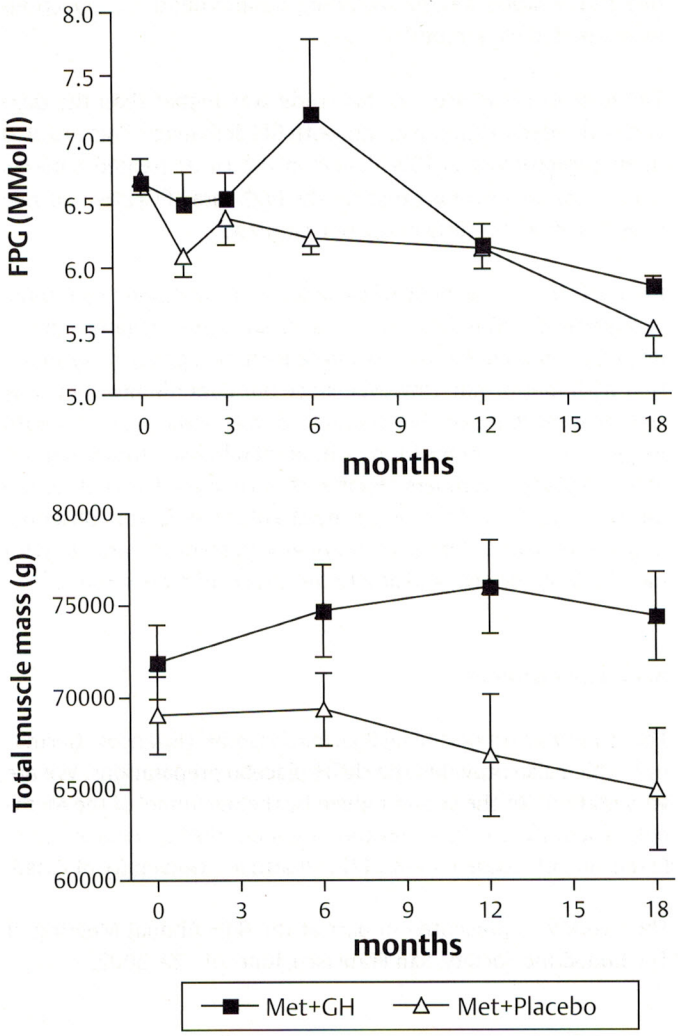

Fig. **3** Courses of fasting plasma glucose (mean ± SEM) and total muscle mass in the two groups of patients treated either with Metformin + GH (n = 12) or with Metformin + Placebo (n = 13). Analysis of the differences between the two groups by repeated measure analysis of variance (RM ANOVA) included the data from all 25 patients (FPG: p = 0.09; total muscle mass: p = 0.16).

in response to the additional administration of rhGH. A statistically significant increase in Lp (a) was observed in both groups without any significant difference between the two groups (Table **2**).

Blood pressure

A slight decrease of systolic and diastolic blood pressure was seen in both treatment groups without statistical difference between the groups (Met + GH: 136 ± 11/88 ± 10 at baseline to 127 ± 13 (WSR p = 0.25)/81 ± 4 (WSR p = 0.38) mmHg after 18 months; Met + Placebo: 126 ± 16/83 ± 11 to 118 ± 9 (WSR p = 0.09)/75 ± 8 (WSR p = 0.11) mmHg).

Total testosterone levels

Serum total testosterone levels significantly increased in both groups after 18 months (Met + GH: 8.57 ± 1.9 to 10.9 ± 3.6 nmol/l, WSR p = 0.03; Met + Placebo: 8.9 ± 1.6 to 14.2 ± 3.5 nmol/l, WSR p = 0.02). Despite a higher increase in the Met + Placebo group, the difference between the two groups did not reach statistical significance (WMW, p = 0.06).

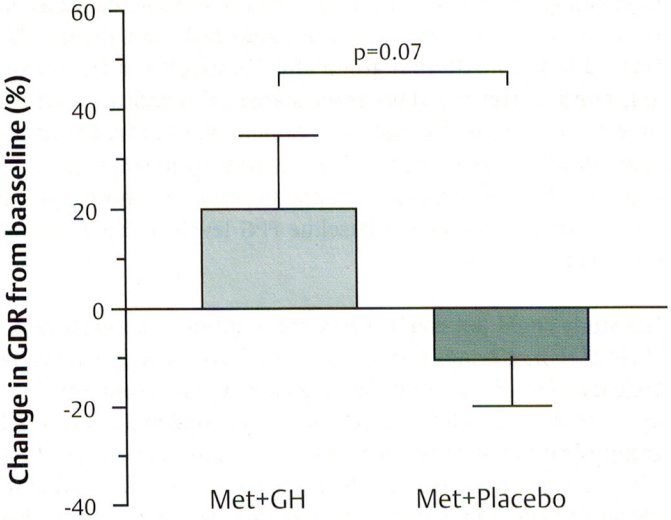

Fig. **4** Percental change of glucose disposal rate (GDR) in the two groups of patients treated either with Metformin + GH or with Metformin + Placebo. The figure gives the results from the 14 patients who completed the study (mean ± SEM) (difference between the two groups: p = 0.07, paired Wilcoxon/Mann/Whitney test).

Discussion

This randomised, double-blind, placebo-controlled trial has provided preliminary evidence that treatment with metformin might be effective in reducing the insulin antagonistic effects of rhGH in patients with metabolic syndrome. However, the additional administration of rhGH to metformin did not have significant beneficial effects on fat metabolism.

Since the insulin antagonistic action of GH has to be regarded as the principal factor for GH induced insulin resistance, and since increases in FPG level during rhGH treatment would primarily be expected in patients with pre-existing insulin resistance [15,22,23], this effect of metformin is especially relevant when treating patients with metabolic syndrome characterised by an insulin-resistant state and high risk of developing type 2 diabetes.

The study included a highly selective male population presenting with obesity and impaired glucose metabolism at baseline. Consistent with earlier findings of disturbances in the neuroendocrine regulation of GH secretion in obesity [10–13], the majority of the patients showed a reduced GH peak in the ARG-GHRH test at baseline.

Despite the fact, that only patients with impaired FPG levels were included in this study, sustained negative effects of rhGH on glucose metabolism were only seen in one patient, and the overall course of FPG and insulin levels did not significantly differ between those patients receiving only metformin and those receiving metformin and rhGH. In agreement with previous studies [3,4,24], we have seen slight increases in FPG levels and glucose levels during oGTT after 6 months of treatment in the group receiving metformin and rhGH, which reached statistical significance for FPG. The overall increase in FPG and AUC glucose levels, however, was transient, both parameters returning to baseline levels during further rhGH and metformin treatment.

Interestingly, GDR as a measure of insulin sensitivity increased in those patients receiving metformin and rhGH and slightly decreased in the metformin group after 18 months of treatment. This effect, however, did not reach statistical significance, which may due to the small sample size. Similar effects of rhGH on insulin sensitivity were observed in the study by Johannsson et al., who investigated obese male patients, who, in contrast to the present study, had normal baseline FPG levels and did not receive metformin [3].

The study could not confirm that the additional administration of rhGH to metformin had favourable effects on body fat. While body fat and waist circumference decreased and insulin sensitivity (GDR) as well as total muscle mass increased in the Met + GH group, the differences between the two groups (Met + GH *vs.* Met + Placebo) were not statistically significant. This may be due to the observation that patients treated with metformin alone also experienced positive effects regarding the course of body composition, a phenomenon known from previous studies [25–27]. Several studies have shown that the administration of rhGH as a monotherapy can reduce total body fat and visceral fat in obese patients due to the lipolytic effect of GH [3,28,29]. However, these patients did not present with impaired glucose tolerance or diabetes mellitus, and did not require antidiabetic drugs such as metformin. In the present study, the risk of the rhGH-induced increase of blood glucose would have been too high in patients with IGT/diabetes mellitus without the additional administration of metformin.

Dyslipoproteinemia is one of the major characteristics of metabolic syndrome and a central finding in patients with growth hormone deficiency [2,30–32]. Previous investigations on the importance of GH as a regulating factor for serum lipids have produced conflicting results in terms of the effects on serum cholesterol, LDL-cholesterol, HDL-cholesterol, and apolipoprotein B [33,34]. We did not observe any statistical differences between the two groups with regard to the courses of total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides or lipoproteins (Table **2**). Considering the fact that administration of GH alone may influence lipid profiles positively, the additional administration of GH to metformin had similar favourable effects as the metformin-treated group. These effects, like the increase in HDL-cholesterol, may be due to the decrease of total body fat concordant to the observations of metabolic syndrome patients that lost body weight [26,27].

Low total testosterone levels were observed in both groups, and are most probably the consequence of increased body weight [35], accumulation of visceral fat [36], and patient age [37]. The increase of total testosterone levels in both groups may be related to the effects of a reduced total body fat on testosterone and SHBG levels [33], and are most probably not due to direct effects of metformin [38,39] or rhGH [40].

One shortcoming of the present study is the high number of dropouts. The dropout rate was similar in the two treatment groups, and most of the dropouts were due to non-compliance. Since most of the dropouts due to non-compliance occurred after the first 12 months of treatment, the high dropout rate is partly due to the study design, including double-blind s.c. injections over a period of 18 months.

The dose of rhGH used in this study was higher than the dose currently used in adult patients with GH deficiency. This resulted in supraphysiological IGF-I levels in the rhGH treated patients and is also the obvious cause for the high rate of GH related side effects during the early phase of treatment.

In conclusion, treatment of patients with metabolic syndrome and elevated FPG levels did not cause sustained negative effects on glucose metabolism or insulin sensitivity if given in combination with metformin. However, since our data did not show any significant differences between the two treatment groups with respect to body composition or lipid metabolism, future studies including larger numbers of patients have to clarify whether the positive effects of rhGH on cardiovascular risk factors observed in patients with GH deficiency are also present in patients with metabolic syndrome, and add to the effects of metformin.

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