Effects on insulin sensitivity and body composition of combination therapy with growth hormone (GH) and insulin-like growth factor-I (IGF-I) in GH deficient adults with type 2 diabetes

Clinical Trial registration number: NCT 01020955

Trial information

The study was a 6 months randomised placebo controlled trial. All participants received rhGH treatment (NutropinAq®) (0.15 mg/day for 1 month, 0.3 mg/day for 5 months) and were randomised to rhIGF-I (Increlex®) or placebo (15 µg/kg/day for 1 month and 30 µg/kg/day for 5 months).
Only adults with verified GHD and non-insulin treated type 2 diabetes were included. Patients already on GH replacement therapy discontinued GH treatment three weeks prior to study entry.
Specific oral anti-diabetic medications (glucose lowering therapy, antihypertensive and lipid lowering therapy) were unchanged throughout the study period.
The regional committee for medical ethics in Stockholm (Karolinska Institute) approved the study, and all patients consented to study participation prior to sample collection and examinations.

Patients and methods

Nine men and five women with known pituitary diseases of different aetiologies, confirmed GHD and type 2 diabetes participated. All had adult onset GHD. Three had isolated GHD. Eleven were treated with GH and 11 were on stable replacement for other pituitary insufficiencies. Thirteen were treated with oral anti-diabetics, one with lifestyle intervention, 11 received medical treatment for hypertension, four patients were treated for hypercholesterolemia.

Anthropometry and body composition

Total body fat (FM), fat free body mass (FFM) and total body water (TBW) were calculated from measurements of bioelectrical impedance. Examination of abdominal fat mass was performed with computed tomography (CT). The patients were scanned at baseline and six months, using a 16 slice scanner (GE LightSpeed pro 16). The basic thin slices were combined for volume calculations. Abdominal scans were made at L2-L3 level, and total abdominal fat volume (TF) and visceral abdominal fat volume (VF) measured. Subcutaneous abdominal fat volume (SF) was calculated by subtracting VF from TF. Measurements of thigh fat volumes were made midway between the right greater trochanter and the joint facet of the lateral condyle.

Euglycemic hyperinsulinemic clamp (clamp)

The clamp was performed according to De Fronzo et al. Intravenous catheters were inserted into the right arm for insulin/glucose infusion. Insulin Actrapid [40 mU/m^2/min] (NovoNordisk A/S, Copenhagen, Denmark) was infused along with 20 % glucose (Fresenius Kabi, Stockholm, Sweden) during 120 min. The rate of glucose infusion was adjusted to achieve and maintain a blood glucose level of 5.0 mmol/L. Whole-body insulin sensitivity (M-value) was calculated from the amount of glucose infused during the last 30 min of the clamp divided by body weight (kg) and period (min) and expressed as mg/kg/min.

Compliance

Empty ampoules collected and returned by the patients were calculated as an indicator for compliance.

Baseline characteristics

Eight patients were randomised to treatment with GH and IGF-I, six to GH and placebo. No differences in study parameters between the groups were seen. (Table 1).

Results at one, three and six months

IGF-I and IGF-I SDS increased in both groups (p=0.001) with the highest increase (median 276 µg/L and 4.8) in the group treated with both GH and IGF-I compared to the group treated with GH and placebo (median 121 µg/L and 2.5). No changes in BMI, waist circumference, blood pressure, pulse, HbA1C, total-, LDL- and HDL-cholesterol, TG, total adiponectin or IGFBP-1 within or between groups were recorded during the study. Two patients withdrew at three months.

Comparison between baseline and 6 months

No changes were noticed in FM or TBW. Percent FFM increased by 4.4 (ns) in the GH and IGF-I treated group compared to -0.4% (ns) in the GH and placebo treated group (p= 0.03 for delta values between groups). Examinations with CT showed no changes in fat mass in thigh, TF or VF, while a decrease in SF by -61ml (ns) was seen in the GH and IGF-I treated group compared to an increase of +23 ml (ns) in the GH and placebo group (p=0.04 for delta values between groups). Insulin sensitivity was low as calculated from clamp (median M-value in the GH and IGF-I treated group 2.6 mg/kg/min, n=4 and in the GH and placebo treated group 5.0 mg/kg/min, n=5; ns between groups). A positive effect was seen in the GH and IGF-I group by 1.4 mg/kg/min (ns), while a negative effect was seen in the GH and placebo treated group by -1.5 mg/kg/min (ns) (p=0.02 for delta values between groups).

Safety parameters, adverse effects and compliance

No changes in safety parameters were seen. In the GH and IGF-I treated group two men dropped out at three months because of fatigue and alcohol abuse, respectively. During the study one male patient was treated with penicillin due to tonsillitis. Otherwise no adverse events occurred. In particular, none of the patients in the group treated with GH and IGF-I developed hypoglycaemia or parotid tenderness.
For the patients who completed the study, compliance was excellent.

Summary

In these patients with GHD and type 2 diabetes positive effects on insulin sensitivity, SF and percent FFM were recorded in the patients receiving the combined treatment with GH and IGF-I for six months. The treatment was well tolerated and no safety issues occurred. Effects of the combined treatment were positive but limited and taking into account the need of an extra daily injection it might be an advantageous treatment option in a few selected patients only.

Table 1
Baseline characteristics (median and range) in 14 adults with growth hormone (GH) deficiency and diabetes type 2 randomised to treatment with GH and insulin-like growth factor I (IGF-I) or GH and placebo

	GH and IGF-I (n=8)	GH and Placebo (n=6)
Age (years)	55.5 (36, 65)	63.5 (48, 69)
Gender (male/female)	5/3	4/2
IGF-I (µg/L)[1]	111 (77, 24.2)	114 (30, 206)
IGF-I SDS	-1.2 (-2.6, -1.1)	-0.8 (-5.3, -0.8)
BMI (kg/m2)[2]	35.6 (27.9, 47.2)	31.9 (25.6, 45.8)
Waist (cm)	116 (101, 138)	112 (98, 113)
Blood pressure	138/88 (112/81, 144/96)	137/84 (115/70, 160/100)
f-glucose (mmol/L)[3]	7.2 (5.2, 9.7)	6.6 (4.8, 8.1)
HbA1c (%)	5.7 (5.2, 7.1)	6.0 (5.2, 5.6)
Total cholesterol (mmol/L)	5.3 (3.6, 6.3)	4.9 (3.3, 5.5)
HDL-cholesterol (mmol/L)[4]	0.9 (0.8, 1.4)	0.9 (0.4, 1.0)
LDL-cholesterol (mmol/L)[5]	2.7 (1.6, 4.2)	3.2 (2.0, 4.3)
Triglycerides (mmol/L)	1.75 (0.9, 6.3)	1.75 (1.0, 2.4)
Adiponectin (mg/L)	4.5 (2.7, 7.2)	3.6 (2.8, 4.9)
IGFBP-1 (µg/L)[6]	21 (7, 49)	25 (13, 60)
Fat Mass (kg)[7]	35.1 (23.8, 63.9)	29.7 (24.8, 84.2)
Fat Free Mass (kg)[7]	66.8 (54.7, 77.1)	66.2 (45.1, 80.4)
Total abdominal fat (ml)[8]	1489.5 (1194.9, 2623.8)	1356.0 (1011.3, 2294.7)
Visceral fat (ml)[8]	588.1 (330.5, 887.9)	664.1 (349.0, 743.8)
Subcutaneous fat (ml)[8]	910.2 (654.5, 1980.9)	744.3 (608.2, 1580.9)
Thigh fat (ml)[8]	406.1 (176.0, 1446.9)	278.0 (56.8, 1123.7)
M-value (mg/kg/min)[9]	2.6 (0.5, 4.5)	5.0 (0.5, 6.0)

[1]IGF-I: Insulin-like growth factor I
[2]BMI: Body mass index
[3] fasting glucose
[4]LDL-C: Low density lipoprotein cholesterol
[5]HDL-C: High density lipoprotein cholesterol
[6]IGF binding protein 1
[7]As evaluated with bio impedance
[8]As measured with computed tomography
[9]As calculated from euglycemic hyperinsulinemic clamp