Effects of growth hormone on insulin resistance and atherosclerotic risk factors in obese type 2 diabetic patients with poor glycaemic control

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Summary

Objective We aimed to evaluate the combined effects of GH treatment and diet restriction on lipolysis and anabolism, insulin resistance and atherosclerotic risk factors in obese patients with type 2 diabetes mellitus (T2DM).

Subjects This randomized, double-blind, placebo-controlled study included 24 obese T2DM patients (male : female = 12 : 12, mean age 53.7 ± 7.2 years) with poor glycaemic control (fasting plasma glucose 10.67 ± 1.21 mmol/l, HbA1c 9.9 ± 2.3%). Sixteen of these patients were treated with recombinant human GH (1–1.5 units/day, 5 days/week) while undergoing diet restriction and exercise for 12 weeks.

Methods Anthropometric and bioelectrical impedance measurements were undertaken to determine the lean body mass and total body fat. Computed tomography (CT) was performed to estimate visceral and subcutaneous fat distribution at the umbilicus level and the muscle area of the midthigh. Insulin resistance was measured by the insulin tolerance test (ITT) and by the homeostasis model assessment of insulin resistance (HOMA-IR).

Results The ratios VSR (visceral fat area/subcutaneous fat area) and VMR (visceral fat area/thigh muscle area) were significantly decreased in the GH-treated group compared to the control group. An increase in lean body mass was observed in the GH-treated group. Levels of total cholesterol, triglyceride, free fatty acid (FFA), fibrinogen, and plasminogen activator inhibitor-1 (PAI-1) were significantly decreased after GH treatment. Fasting glucose levels decreased similarly (P < 0.05 ANOVA) in both groups during the treatment period. Fasting C-peptide levels significantly increased, whereas insulin levels significantly decreased, in the GH-treated group, but no changes were observed in the control group. The insulin sensitivity index (ISI) was significantly increased in the GH-treated group (1.3 ± 1.4 vs. 1.9 ± 1.0%/min, P < 0.05).

Conclusions GH treatment in obese T2DM patients with poor glycaemic control is beneficial in decreasing the amount of visceral fats, and may therefore result in improvements in insulin resistance, atherosclerotic risk factors and dyslipidaemia.

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Introduction

Type 2 diabetes mellitus (T2DM) and impaired glucose tolerance, in addition to obesity, may contribute to the alteration of GH secretion, as even lean patients with T2DM exhibit an attenuated GH response to GH releasing hormone (GHRH). Moreover, it has been proposed that a low level of IGF-I, a peptide that is thought to mediate the effects of GH, predicts a worsening of insulin-mediated glucose uptake, while restoration of IGF-I level enhances insulin sensitivity in patients with T2DM.

Insulin resistance is commonly observed in obese subjects and acts as an independent risk factor for the development of T2DM. In particular, an increment of visceral adiposity is associated with most of the abnormal metabolic pathways predisposing to T2DM, including increased peripheral insulin resistance. Considering that skeletal muscle is the elementary tissue responsible for glucose uptake, an increase in skeletal muscle mass may constructively influence insulin sensitivity through its capacity to take up a glucose load. Therefore, the most effective method to improve insulin sensitivity in obese T2DM patients would be a manipulation that could accelerate visceral fat loss and conserve or increase lean body mass.

Diet restriction as a fundamental management for obesity is complicated by the protein catabolism associated with undesirable loss of skeletal muscle mass. GH retains a positive nitrogen balance during dietary restriction by increasing IGF-I. However, higher doses and longer duration of GH treatment can lead to a substantial impairment of insulin sensitivity, which may result in hyperinsulinaemia. Although additive to the anabolic actions of GH, hyperinsulinaemia abrogates the lipolytic actions of GH due to lipogenesis stimulated by insulin.

In this study, we investigated whether restoration of normal IGF-I levels by low-dose GH treatment combined with diet restriction
could play a possible therapeutic role in improving insulin sensitivity in patients with T2DM.

Subjects and methods

Subjects

This study included 24 patients with T2DM [male : female = 12 : 12, mean age 53.7 ± 7.2 years, waist circumference > 90 cm (male) or 80 cm (female)] from the Diabetes Centre of the Severance Hospital. The study protocol was approved by the ethical committee at Yonsei University College of Medicine, and informed consent was obtained from all patients.

The inclusion criteria were the following: (1) fasting plasma glucose > 7.8 mmol/l, (2) the absence of diabetic retinopathy or microalbuminuria, (3) below the normal range of IGF-I, and (4) a GH level < 5 μg/l after the stimulation of a hypoglycaemic state (< 50 mg/dl after an intravenous bolus injection of regular insulin (Humulin-R, Eli Lilly, USA, 0.2–0.3 U/kg of body weight)). Patients with < 0.33 nmol/l of fasting C-peptide or > 2.5%/min of insulin sensitivity index (ISI) were excluded, in order to select T2DM patients < 0.33 nmol/l of fasting C-peptide or > 2.5%/min of insulin sensitivity index (ISI). Patients with fasting glucose > 7.8 mmol/l, (2) the absence of diabetic retinopathy or microvascular disease, (3) below the normal range of IGF-I, and (4) a GH level < 5 μg/l after the stimulation of a hypoglycaemic state (< 50 mg/dl after an intravenous bolus injection of regular insulin (Humulin-R, Eli Lilly, USA, 0.2–0.3 U/kg of body weight)). Patients with < 0.33 nmol/l of fasting C-peptide or > 2.5%/min of insulin sensitivity index (ISI) were excluded, in order to select T2DM patients with insulin resistance. No patients had used any hormonal or lipid-lowering drugs within 60 days prior to commencement of the study.

Methods

The study was a 12-week, randomized, double-blind, placebo-controlled trial of the administration of recombinant human GH (Norditropin®, Novo Nordisk). The daily dose of 1 IU GH (1 mg = 3 IU) was administered subcutaneously before bedtime five times a week, excluding weekends, for 12 weeks. Serum IGF-I level was measured monthly in order to achieve the optimal dose of GH. If the level of IGF-I was not within the normal sex- and age-adjusted range of reference, an additional 0.5 unit of GH was administered. The placebo vials contained the same vehicle as the GH vials and both preparations were visually indistinguishable. Compliance was assessed by counting the returned empty vials.

All of the patients were instructed to stay on a daily diet of 25 kcal/kg ideal body weight and to exercise (200 kcal/day), and patient compliance was confirmed by diabeticians. All patients were treated with sulfonylurea for glucose control.

Body weight and height were measured in the morning with participants wearing light clothing. Body mass index (BMI) was calculated as the weight (in kilograms) divided by the height (in metres) squared. Waist circumference was measured with a soft tape, midway between the lowest rib and the iliac crest, while patients were standing.

Measurement of body composition

Body composition was determined using a bioelectric impedance meter (Bioimpedance method, Inbody 3-0, Biospace, Korea), and the results were expressed as the percentage of fat mass.

A computed tomography (CT) scan was performed using a CT Max II (General Electric Co., USA) to measure visceral and subcutaneous fat areas at the level of the umbilicus. The adipose tissue was defined as having a density of −150 to −50 Hounsfield units and was divided into visceral fat tissue (the inner portion) and subcutaneous fat tissue (the outer portion) according to its position relative to the peritoneal membrane. The VSR was calculated as the ratio of visceral fat area to subcutaneous fat area. Measurements of the skeletal muscle area (Hounsfield number, −49 to 100) from the middle of the femur yielded the VMR (ratio of visceral fat area to thigh muscle area).

Measurement of the biochemical profiles

Blood samples were taken after 8 h of fasting on Monday prior to treatment and 1 week after the end of the treatment for measurement of glucose, HbA1C, C-peptide, insulin, total cholesterol, triglyceride, high density lipoprotein (HDL)-cholesterol, free fatty acid (FFA), fibrinogen, plasminogen activator inhibitor-1 (PAI-1) and IGF-I levels. Additional samples were taken at 4, 8 and 12 weeks after commencing the treatment for the measurement of glucose and IGF-I levels, and 4 weeks after the end of the treatment for the measurement of glucose.

Plasma glucose was measured by the glucose oxidation technique on an autoanalyser (Beckman, Fullerton, CA, USA). HbA1C levels were analysed using high performance liquid chromatography (Variant II, Bio-Rad, Hercules, CA, USA); the normal range was 4.0–6.0%. Insulin and C-peptide were measured by an immunoradiometric assay (IRMA kit, Dainabot, Japan) and radioimmunoassay (RIA kit, Daiichi, Japan), respectively. Total cholesterol and triglyceride levels were measured using an enzymatic method (Roche Diagnostics, Basel, Switzerland) with an autochemical analyser (Hitachi 747, Nakashi, Japan). HDL-cholesterol was assayed using a selective inhibition test (Daichii, Tokyo, Japan). Low density lipoprotein (LDL)-cholesterol was calculated according to the Friedwald formula. FFA levels were determined by colorimetry. PAI-1 was measured by an enzyme immunoassay (Biopool TintElize kit, Ventura, CA, USA). Fibrinogen was measured in citrated plasma by a modified clot-rate assay using a Pacific Hemostasis Assay Set (Hummersville, NC, USA). This technique was based on the original method of Clauss. IGF-I was measured using an IRMA kit (Diagnostic System Laboratories, Webster, TX, USA) with acid/ethanol extraction; its sensitivity was 0.3 mg/l, and intra- and interassay coefficients of variation (CVs) were less than 10%. Serum samples were separated by centrifugation and stored at −20 °C until analysis.

Measurement of insulin resistance

Insulin resistance was measured by the insulin tolerance test (ITT) and by the homeostasis model assessment of insulin resistance (HOMA-IR) as follows: HOMA-IR = fasting insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5.

The ITT was carried out 8 h after an overnight fast. Venous blood samples were collected 1 min prior to an intravenous bolus injection of regular insulin (Humulin-R, Eli Lilly, USA, 0.1 U/kg of body weight) and 3, 6, 9, 12 and 15 min after injection. The samples were collected in tubes containing ethylenediaminetetraacetic acid (EDTA) and NaF and centrifuged for the immediate determination of plasma glucose levels. At the end of the ITT, a continuous 30-min
infusion of 100 ml of a 20% glucose solution was administered intravenously. None of the patients had symptoms of hypoglycaemia during or after the test.

The ISI was calculated as described previously. The ISI was derived by linear regression from the rate of the fall of the log glucose value between 3 and 15 min. \( t_{1/2} \) was calculated when the baseline glucose level reached 50% of the initial value, and the ISI was calculated from the equation: 

\[
\text{ISI} = \frac{0.693}{t_{1/2}} \times 100 \quad \text{%/min}.
\]

### Statistical analysis

Results were expressed as the mean ± SD. Comparisons were made between the GH-treated group and the control group using an unpaired Mann–Whitney U-test. The significance of an intradividual change of variables was tested using repeated measures of the analysis of variance (ANOVA). Statistical analyses were conducted using SPSS for Windows, version 11·0 (SPSS Inc., Chicago, IL, USA), and the level of significance used was \( P < 0.05 \).

### Results

The two groups of poorly controlled diabetic subjects were matched with regard to sex and age. Prior to GH treatment, the two groups did not differ in the duration of T2DM, blood pressure, HbA1c levels, glucose levels, C-peptide levels, insulin levels, BMI, waist circumference, body fat percentage and lean body mass (Tables 1 and 2).

#### Effect of GH treatment on weight loss and body composition

BMI during the entire study was equivalent in both groups. However, the waist circumference and body fat percentage were significantly reduced in the GH-treated group, while no such differences were apparent in the control group. In terms of lean body mass, measured by impedance, a significant increase was observed in the GH-treated group (52·1 ± 8·2 kg vs. 55·3 ± 7·4 kg, \( P < 0.05 \)), while no difference was observed in the control group (52·9 ± 6·3 kg vs. 53·1 ± 7·2 kg, \( P > 0.05 \)). GH treatment resulted in significant reductions in the visceral fat area (162·3 ± 48·5 cm\(^2\) vs. 145·9 ± 39·2 cm\(^2\), \( P < 0.05 \)), VSR and VMR. However, no such changes were observed in the control groups (Table 2).

#### Effect of GH treatment on biochemical markers

GH treatment resulted in an increase in IGF-I level in the GH-treated group. Total cholesterol, triglyceride (from 2·240 ± 0·413 mmol/l to 1·867 ± 0·413 mmol/l, \( P < 0.05 \)), and LDL-cholesterol levels were significantly decreased and HDL-cholesterol level was increased after GH treatment in the GH-treated group, but these levels did not differ in the duration of T2DM, blood pressure, HbA1c levels, glucose levels, C-peptide levels, insulin levels, BMI, waist circumference, body fat percentage and lean body mass (Tables 1 and 2).

### Table 1. Baseline clinical characteristics of study subjects

<table>
<thead>
<tr>
<th></th>
<th>GH-treated group*</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>8/8</td>
<td>4/4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53·1 ± 7·2</td>
<td>54·2 ± 7·1</td>
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<tr>
<td>DM duration (years)</td>
<td>11·4 ± 7·2</td>
<td>10·9 ± 6·2</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>135·2 ± 21·1</td>
<td>138·1 ± 18·1</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>85·8 ± 16·2</td>
<td>88·2 ± 17·6</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>10·0 ± 0·2</td>
<td>10·0 ± 0·2</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>9·7 ± 2·3</td>
<td>9·7 ± 2·2</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>10·847 ± 1·271</td>
<td>10·508 ± 0·960</td>
</tr>
<tr>
<td>Insulin (pmol/l)</td>
<td>0·48 ± 0·11</td>
<td>0·50 ± 0·14</td>
</tr>
<tr>
<td>Insulin (pmol/l)</td>
<td>58·8 ± 15·0</td>
<td>58·2 ± 16·2</td>
</tr>
</tbody>
</table>
| Values are presented as the mean ± SD. DM, diabetes mellitus; BP, blood pressure. *No statistically significant differences between the groups (\( P > 0.05 \)).

### Table 2. Effect of GH treatment on body composition and insulin resistance

<table>
<thead>
<tr>
<th></th>
<th>GH-treated group (( N = 16 ))</th>
<th>Control group (( N = 8 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
<td>Change</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>28·3 ± 4·1</td>
<td>28·1 ± 4·0</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>96·2 ± 6·3</td>
<td>93·5 ± 5·2*</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>35·4 ± 6·6</td>
<td>31·4 ± 6·3*</td>
</tr>
<tr>
<td>LBM (kg)</td>
<td>52·1 ± 8·2</td>
<td>55·3 ± 7·4*</td>
</tr>
<tr>
<td>Visceral fat area (cm(^2))</td>
<td>162·3 ± 48·5</td>
<td>145·9 ± 39·2*</td>
</tr>
<tr>
<td>SC fat area (cm(^2))</td>
<td>184·4 ± 51·3</td>
<td>187·0 ± 45·6</td>
</tr>
<tr>
<td>Thigh muscle area (cm(^2))</td>
<td>121·1 ± 34·1</td>
<td>126·9 ± 28·6</td>
</tr>
<tr>
<td>VSR</td>
<td>0·888 ± 0·26</td>
<td>0·780 ± 0·24*</td>
</tr>
<tr>
<td>VMR</td>
<td>1·34 ± 0·37</td>
<td>1·15 ± 0·43*</td>
</tr>
<tr>
<td>ISI (%/min)</td>
<td>1·3 ± 1</td>
<td>1·9 ± 1·0</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>3·95 ± 1·12</td>
<td>2·24 ± 0·98*</td>
</tr>
</tbody>
</table>
| Values are presented as mean ± SD. BMI, body mass index; WC, waist circumference; LBM, lean body mass; SC, subcutaneous; VSR, visceral fat area/subcutaneous fat area ratio; VMR, visceral fat area/thigh muscle area; ISI, insulin sensitivity index; HOMA-IR, homeostasis model assessment of insulin resistance. *\( P < 0.05 \) before vs. after treatment in each group. †\( P < 0.05 \) control group vs. GH-treated group after treatment.
remained the same in the control group. After GH treatment, fasting C-peptide level was increased significantly in the GH-treated group (0.48 ± 0.11 nmol/l vs. 0.56 ± 0.10 nmol/l, P < 0.05) but not in the control group (0.50 ± 0.14 nmol/l vs. 0.48 ± 0.11 nmol/l, P > 0.05). The fasting insulin level was significantly decreased in the GH-treated group (P < 0.05) but no such change was observed in the control group. FFA level was decreased significantly from 6.753 ± 2.452 g/l prior to treatment to 6.001 ± 2.232 g/l after treatment (P < 0.05) in the GH-treated group, but no significant reduction was apparent in the control group (6.619 ± 3.012 g/l vs. 6.211 ± 2.122 g/l, P > 0.05). Moreover, there were significant decreases in fibrinogen and PAI-1 levels in the GH-treated group, but not in the control group (Table 3).

Effect of GH treatment on insulin resistance and glucose control

The ISI was significantly increased in the GH-treated group from 1.3 ± 1.4%/min prior to treatment to 1.9 ± 1.0%/min after treatment (P < 0.05), indicating a reduced insulin resistance. No such modification was observed in the control group (1.3 ± 1.1%/min vs. 1.5 ± 0.9%/min, P > 0.05). As predicted from the significant fall in fasting insulin levels following GH treatment, the HOMA-IR was significantly decreased in the GH-treated group, and no such change was observed in the control group (Table 2).

Fasting glucose levels tended to decrease in both groups during the treatment period, and a significant decrease was observed after 8 weeks of treatment in both groups. No significant change was detected in glucose levels at 16 weeks (4 weeks after the last injection), as compared to changes seen at 12 weeks. No significant differences were found in glucose levels between the GH-treated group and the control group during treatment (Fig. 1). Furthermore, HbA1c levels were significantly decreased in both groups (Table 3).

Discussion

This study demonstrates that low-dose GH treatment combined with diet restriction is effective in reducing visceral adipose tissue, VSR and VMR, with a consequent improvement in insulin sensitivity in obese patients with poorly controlled T2DM. Considering the well-documented lipolytic effect of GH,14,15 the finding of a preferential reduction in visceral fat deposits observed in this study is consistent with the previous reports demonstrating that the GH-stimulated abrogation in the anti-lipolytic effects of insulin is selective for specific adipose tissue deposits.16,17 GH enhancement of lipolytic activity in adipose tissue combined with a reduction in triglyceride accumulation by inhibition of lipoprotein lipase activity appears to be the major mechanism by which GH treatment results in a reduction in total fat mass.18

There is the possibility that the reduced insulin resistance noted in the GH-treated patients may be associated with an improvement in endogenous insulin secretion. In fact, we detected a small but significant increase in fasting C-peptide in the GH-treated group, suggesting an increase in endogenous insulin secretion. This might be attributed to the reduced FFA levels19 or to a proliferation of β-cells.20 Whether this apparent increase in insulin secretion in the GH-treated group is biologically significant is uncertain, as the decrement of fasting glucose was similar in both the treated and untreated GH subjects.

GH is known to cause insulin resistance in liver and peripheral tissue.21 As hyperinsulinaemia induced by insulin resistance has anti-lipolytic effect, it may attenuate the lipolytic effect of GH. Snyder et al.8 observed that a higher dose of GH increased urinary excretion of C-peptide and that there was an inverse correlation between the degree of fat loss and urinary C-peptide excretion during GH treatment. In their study, they showed that urinary C-peptide excretion rate correlated positively with dose of GH. Therefore, they stated that effective lipolysis can be expected when GH is given at a dose that

Table 3. Changes in biochemical characteristics before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>GH-treated group (N = 16)</th>
<th>Control group (N = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>TC (mmol/l)</td>
<td>6.217 ± 0.688</td>
<td>5.984 ± 0.680*</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>2.240 ± 0.413</td>
<td>1.867 ± 0.410*</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>0.915 ± 0.197</td>
<td>1.019 ± 0.163*</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>4.854 ± 0.435</td>
<td>4.592 ± 0.446*</td>
</tr>
<tr>
<td>C-peptide (nmol/l)</td>
<td>0.48 ± 0.11</td>
<td>0.56 ± 0.10*</td>
</tr>
<tr>
<td>Insulin (pmol/l)</td>
<td>58.8 ± 15.0</td>
<td>43.7 ± 17.2*</td>
</tr>
<tr>
<td>FPG (mmol/l)</td>
<td>10.847 ± 1.271</td>
<td>8.275 ± 0.575*</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>10.0 ± 2.3</td>
<td>8.1 ± 1.3*</td>
</tr>
<tr>
<td>FFA (g/l)</td>
<td>6.753 ± 2.452</td>
<td>6.001 ± 2.232*</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>4.322 ± 0.832</td>
<td>2.892 ± 0.812*</td>
</tr>
<tr>
<td>PAI-1 (ng/ml)</td>
<td>43.1 ± 7.3</td>
<td>26.2 ± 6.1*</td>
</tr>
<tr>
<td>IGF-1 (µg/l)</td>
<td>182.2 ± 83.2</td>
<td>389.2 ± 71.3*</td>
</tr>
</tbody>
</table>

Values are presented as the mean ± SD. TC, total cholesterol; TG, triglyceride; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; FPG, fasting plasma glucose; FFA, free fatty acid; ISI, insulin sensitivity index; PAI-1, plasminogen activator inhibitor-1.

*P < 0.05 before vs. after treatment in each group. †P < 0.05 control group vs. GH-treated group after treatment.
does not cause hyperinsulinaemia. In our study, fasting insulin levels fell after GH treatment. It is well recognized that the clearance of insulin is significantly reduced in obesity, particularly in those subjects with fatty livers, which occurs frequently in obese T2DM subjects. Therefore, the increased clearance of insulin after GH treatment would have accounted for the lower peripheral insulin levels and for the apparent improvement in the HOMA-IR.

In our study, fasting glucose levels declined in the GH-treated group during the treatment period. Previous studies examining the effects of GH on glucose metabolism have yielded contrasting results. Some investigators demonstrated acute insulin-like effects and improvement in postload glucose tolerance without a change in β-cell function. Meanwhile, others demonstrated diabetogenic effects at the insulin receptor and postreceptor sites. In some studies, GH treatment of patients with metabolic syndrome did not cause sustained negative effects on glucose metabolism or insulin sensitivity if given in combination with metformin. These conflicting results raise the question of whether or not various dosages of GH have distinct, independent effects on glucose homeostasis.

We found that the reductions in fasting glucose and HbA1c levels were similar in the GH-treated and the placebo group. This suggests that over the 3 months of diet/exercise treatment, the addition of GH therapy failed to influence the glycaemic control in these T2DM obese subjects, despite the decrease in visceral fat and insulin resistance. This may arise because the effect of the sulfonylureas on plasma glucose is so much more dominant on plasma glucose that it may mask any effect of GH with regard to glycaemic control.

Consistent with the ability of GH to stimulate hepatic LDL-receptor activity, the LDL-cholesterol level was decreased in the GH-treated group. Furthermore, PAI-1 and fibrinogen, which are known to be closely related to insulin resistance, were significantly decreased by GH treatment. However, more studies are needed to further investigate the possibility of the beneficial effect of GH treatment on atherosclerosis.

The present study had limitations in that subject numbers were small. In addition, we estimated insulin resistance by the ITT and HOMA-IR, but accurate peripheral insulin sensitivity cannot be assessed by these tests. The ITT is mainly a test of hepatic insulin sensitivity. Thus, our significant rise in ISI mainly reflects an improvement in hepatic sensitivity. Therefore, it would have been preferable to use more invasive techniques such as the hyperinsulinaemic euglycaemic clamp to assess hepatic and peripheral insulin sensitivity.

Nevertheless, we have demonstrated that the restoration of IGF-I level by GH treatment in obese T2DM patients can be beneficial not only by decreasing visceral adipose tissue but also by modifying atherosclerotic risk factors with a consequent decrease in insulin resistance. However, further large-scale controlled trials are required.

Acknowledgements
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into the anthropometric classification of fat distribution shown by computed tomography. *British Medical Journal*, 290, 1692–1694.


