CLINICAL STUDY

Effect of short-term GH and testosterone administration on body composition and glucose homoeostasis in men receiving chronic glucocorticoid therapy

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Abstract

Objective: Long-term pharmacological glucocorticoid (GC) therapy leads to skeletal muscle atrophy and weakness. The objective of this study was to investigate whether short-term treatment with GH and testosterone (T) can increase lean mass without major impairment of glucose homoeostasis in patients on GC therapy.

Design, materials and methods: This was a prospective, open-label, randomised, crossover study. Twelve men (age 74 ± 6 years) on chronic GC treatment participated. The effects of 2 weeks’ treatment with GH, testosterone and the combination of both on lean body mass (LBM), appendicular skeletal muscle mass (ASMM), extracellular water (ECW), body cell mass (BCM) and plasma glucose concentrations were investigated.

Results: LBM increased significantly after GH (Δ1.7 ± 1.4 kg; P = 0.007) and GH + testosterone (Δ2.4 ± 1.1 kg; P = 0.003), but not testosterone alone. ASMM increased after all three treatment periods; by 1.0 ± 0.8 kg after GH (P = 0.005), 1.7 ± 0.4 kg after GH + testosterone (P = 0.002) and 0.8 ± 1.0 kg after testosterone (P = 0.018). The increase in ASMM was larger with combined treatment than either GH or testosterone alone (P < 0.05). ECW increased significantly after GH + testosterone by 1.5 ± 2.6 l (P = 0.038) but not after GH or testosterone alone. BCM increased slightly after single and combined treatments, but the changes were not significant. Fasting glucose increased significantly after GH (Δ0.4 ± 0.4 mmol/l, P = 0.006) while both fasting (Δ0.2 ± 0.3 mmol/l, P = 0.045) and post glucose-load (Δ1.8 ± 2.3 mmol/l, P = 0.023) plasma glucose concentrations increased after GH + testosterone.

Conclusions: GH and testosterone induce favourable and additive body compositional changes in men on chronic, low-dose GC treatment. In the doses used, combination therapy increases fasting and postprandial glucose concentration.

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Introduction

Glucocorticoids (GCs) are potent anti-inflammatory and immunosuppressive agents that effectively reduce morbidity in a wide range of inflammatory and autoimmune diseases. However, long-term GC use is often associated with side effects including weight gain, impaired glucose homoeostasis, osteoporosis and muscle and skin atrophy (1). GCs induce protein catabolism by increasing irreversible oxidative loss of protein, resulting in skin thinning and muscle atrophy and weakness (2, 3). To date, no specific treatment is available to prevent or reverse GC-induced protein wasting. Long-term GCs are prescribed to 0.5–0.9% of the general population and as many as 2.5% of elderly subjects (4, 5). Therefore, a substantial number of patients are at risk of muscle atrophy, which is associated with substantial morbidity and increased mortality (6).

GH and testosterone (T) are potent anabolic hormones. GH increases lean body mass (LBM) when administrated to patients with GH deficiency (GHD) (7) and healthy elderly men (8, 9, 10). Similarly, testosterone administration increases LBM in men with acquired hypogonadism (11) and protein synthesis, appendicular skeletal muscle mass (ASMM) and muscle strength in healthy elderly men (9, 10, 12). In patients with...
hypopituitarism, the anabolic actions of GH and testosterone are additive (13).

Early studies provided proof of concept that GH prevents GC-induced protein catabolism (14, 15). However, the doses of GH were markedly supraphysiological and caused substantial hyperglycaemia. Therefore, these GH doses are not a long-term therapeutic option to treat sarcopaenia in patients on long-term GCs, who are already at increased risk of diabetes mellitus. Recently, we undertook a dose-finding study and reported that in elderly women on chronic GC therapy, a GH dose of 0.8 mg daily induced protein anabolism with only a modest increase in fasting glucose (16). However, the metabolic effects of GH are greater in men than in women (17). Furthermore, in men there is a potential to co-administer testosterone, which increases LBM and muscle strength during long-term GC therapy (18, 19).

In this study, we have extended the findings of our previous study to investigate whether the same dose of GH exerts favourable body compositional changes without inducing major perturbation of glycaemic status in men on chronic GC therapy. We have also assessed whether combining GH and testosterone treatment has an additive effect on skeletal muscle mass.

Materials and methods

Patients

Twelve men with polymyalgia rheumatica were recruited from the Department of Rheumatology and Department of Internal Medicine, Sahlgrenska University Hospital. All patients had received treatment with prednisolone for more than 1 year (mean duration 9.3 ± 6.9, range 1.5–20 years), were in remission for at least 6 months and had a stable prednisolone dose in the 3 months before inclusion (mean dose 5.8 ± 1.5, range 5–8.75 mg). Patients with diabetes mellitus, congestive heart failure, uncontrolled hypertension, hepatic dysfunction, serum creatinine >150 μmol/l, a history of cancer or those administered other hormonal treatment were not eligible for inclusion.

Study design

This was a prospective, open-label, randomised, crossover study comparing the effect of GH for 2 weeks, testosterone for 2 weeks and the combination of GH and testosterone for 2 weeks. Each treatment period was followed by a 2-week wash-out period (Fig. 1). GH (Genotropin Mini Quick, Pfizer) was administered s.c. every evening in a dose of 0.8 mg and testosterone (Testogel, Schering) transdermally in a dose of 50 mg daily in the morning. Measurements were performed after a 12-h overnight fast, at baseline and at the end of each treatment period. During the study the subjects were advised to continue their usual activities of daily living.

Ethical considerations

Informed written consent was obtained from all patients. The Regional Ethical Review Board of the University of Gothenburg, Göteborg, Sweden, and the Swedish Medical Products Agency, Uppsala, Sweden, approved the study (EudraCT-number: 2005-003750-10). The study was conducted according to the Declaration of Helsinki.

Anthropometry

Height was measured with an accuracy of 0.5 cm and weight (kg) to one decimal place; BMI was calculated as weight/height² (kg/m²). Waist circumference (WC) was measured in the supine position midway between the iliac crest and the lowest level of the thorax.

Glucose metabolism

Plasma glucose and insulin were measured in fasting state and during an oral glucose tolerance test (OGTT; 75 g glucose). Area under the curve for glucose and insulin was calculated according to the Tai’s model (20). Insulin resistance (IR) was calculated according to the homoeostatic model assessment-insulin resistance (HOMA-IR) from fasting plasma insulin and glucose concentration where the output of the model is calibrated to give a normal IR of 1 (21). Estimates of insulin sensitivity index (ISI) and β-cell function (insulinogenic index (IGI)), based on the OGTT, were calculated as previously described (22, 23).

Body composition

LBM, fat mass, central abdominal fat and bone mineral content (BMC) were measured using dual-energy X-ray absorptiometry (DEXA; Lunar DPX-L, 12 Lunar Corporation, Madison, WI, USA). ASMM was calculated from
lean mass of arms and legs obtained from the DEXA scan (24). Extracellular water (ECW) was measured using the bromide-dilution technique (25). A weighed amount of sodium bromide (2.25 g), diluted in 45 ml of sterile water, was ingested at 0800 h after an overnight 12-h fast. Serum samples were collected before and 3 h after ingestion. Serum bromide was measured by HPLC (Dionex Corp., Sunnyvale, CA, USA). Coefficient of variation (CV) in duplicate samples was 0.7% (within run) and 3.3% (between runs).

Body cell mass (BCM) was calculated according to the four compartment model by subtracting ECW from LBM.

**Indirect calorimetry**

After resting for 30 min, O₂ consumption (VO₂) and CO₂ production (VCO₂) were measured with an open-circuit ventilated hood system (Deltatrac II Metabolic Monitor; Datex Instrumentarium Corp., Helsinki, Finland) over two 20-min periods and averaged. Calibration against standard gases (mixture of O₂ and CO₂) was done before each measurement. Resting energy expenditure (REE) and substrate oxidation rates were calculated using the equations of Weir (26).

**Analytical methods**

Plasma glucose concentration was measured using an enzymatic hexokinase method (GLU, Roche/Hitachi; Roche Diagnostics) with a 4% CV at concentrations between 5 and 15 mmol/l, and serum insulin with an immunometric two-step sandwich method and chemiluminescence technology (Insulin Elecsys, Roche Diagnostics GmbH) with a 10% CV at 6, 20 and 70 mU/L. Total-, LDL- and HDL-cholesterol and triglycerides (TG) in serum were measured by enzymatic method (Roche Diagnostics). The CV for total cholesterol was 3% at serum concentrations between 4 and 6 mmol/l, 4% for LDL at concentrations between 2 and 5 mmol/l, 5% for HDL cholesterol at concentrations between 1 and 2 mmol/l and 4% for TG at concentrations between 1 and 2 mmol/l. Serum IGF1 was measured by an immunoenzymometric assay (Immullite 2500 IGF1, DPC/Siemens Medical Solutions Diagnostics Ltd, Llanberis, Gwynedd, UK), the CV was 12% at 13 nmol/l and 9% at 33 and 100 nmol/l. Serum testosterone was measured by a competitive immunochromatographic method with chemiluminescence technology (Access Testosterone, Beckman-Coulter, Fullerton, CA, USA) and the CV was 10% at 5, 20 and 40 nmol/l. Serum Procollagen III peptide (PIIIP) was measured by an immunoradiometric, two-step sandwich method (RIA-gnost PIIIP kit no OCFK07-PIIIP, Cisbio Bioassays, Codolet, France) and the CV was 5% at 0.9 and 1.1 kU/L, and 7% at 0.7 kU/L.

**Figure 2** Box plots showing change in (A) lean body mass, (B) appendicular skeletal muscle mass and (C) serum procollagen III peptide during treatment with GH for 2 weeks, testosterone (T) for 2 weeks and GH and testosterone in combination for 2 weeks. Boxes represent median and 25th and 75th percentiles, lines 10th and 90th percentiles and dots measurements outside the 10th and 90th percentiles.
**Statistical analysis**

All statistical analyses were performed with PASW statistics, version 17.0 for windows. Normally distributed data are presented as mean ± s.d. and non-normally distributed data as median (25th and 75th percentiles). Wilcoxon-signed rank test was used for within-group comparisons and Mann–Whitney U test for comparisons of change from baseline between groups. A P value of < 0.05 was considered statistically significant.

**Results**

**Subject characteristics**

The mean age was 74 ± 6 years (range 64–85). The patients had received treatment with prednisolone for 9.3 ± 6.9 years (range 1.5–20) at a stable dose of 5.8 ± 1.5 mg (range 5–8.75 mg) for at least 3 months before study entry. Seven patients (58%) had treatment for hypertension, three (25%) for hyperlipidaemia and four (33%) had bisphosphonate treatment.

**Body composition**

LBM was increased significantly by 1.7 ± 1.4 kg (P = 0.007) after treatment with GH and 2.4 ± 1.1 kg (P = 0.003) after GH + testosterone. The increase in LBM after testosterone approached statistical significance (0.9 ± 1.4 kg, P = 0.054). The increase in LBM was greater after GH + testosterone than that with testosterone alone (Fig. 2A). ASMM increased significantly after all three treatment periods: by 1.0 ± 0.8 kg after GH (P = 0.005), 1.7 ± 0.4 after GH + testosterone (P = 0.002) and 0.8 ± 1.0 kg after testosterone (P = 0.018). The increase in ASMM was more marked after combination treatment than with GH and testosterone alone (Fig. 2B). The increase in ECW after GH alone did not reach statistical significance (0.7 ± 1.1 l, P = 0.065) but increased after GH + testosterone by 1.5 ± 2.6 l (P = 0.038). There was no significant change in ECW after testosterone alone (0.0 ± 2.0 l, P = 0.583) (Table 1). BCM did not change significantly during any treatment period although the increase with GH approached statistical significance (1.0 ± 1.9 kg, P = 0.065) (Table 1). Weight, WC, fat mass and central abdominal fat did not significantly change during any treatment period (Table 1).

**S-PIIIP, IGF1 and testosterone**

S-PIIIP increased after GH + testosterone (0.83 ± 0.40; P = 0.016) and approached statistical significance after GH (0.64 ± 0.33; P = 0.077) and testosterone alone (0.60 ± 0.23; P = 0.075). The increase from baseline was more marked after GH + testosterone than with testosterone alone (P = 0.020) (Fig. 2C). Serum IGF1 concentrations were increased during GH and GH + testosterone but did not change with testosterone alone (Table 1). Ten and nine patients recorded a serum IGF1 concentration > 2 s.d. above the sex- and age-specific reference range after GH and GH + testosterone respectively. Serum testosterone concentration increased during testosterone and GH + testosterone but not with GH alone (Table 1). Three patients recorded a serum testosterone concentration > 2 s.d. above normal value: one after testosterone, one after GH + testosterone and one during both testosterone and GH + testosterone.

| Table 1 | Anthropometry, body composition, resting energy expenditure, substrate oxidation and serum levels of IGF1 and testosterone (T) during treatment with testosterone, GH and combination of GH and testosterone. Data is presented as mean ± s.d. or median (25th and 75th percentiles). |
|----------------|-----------------|---|-----------------|
| **Baseline** | **Testosterone** | **GH** | **Testosterone + GH** |
| BMI (kg/m²) | 26.0 ± 3.3 | 26.2 ± 3.5 | 26.3 ± 3.3 | 26.5 ± 3.3 a |
| Waist (cm) | 99.7 ± 8.2 | 98.0 ± 9.2 | 99.0 ± 8.9 | 100.0 ± 9.1 |
| Total body mass (kg) | 80.3 ± 12.0 | 81.1 ± 13.0 | 81.8 ± 13.0 | 82.4 ± 12.6 a |
| TBF (kg) | 24.3 ± 8.3 | 24.3 ± 9.1 | 24.1 ± 8.8 | 24.0 ± 8.0 |
| CF (kg) | 14.5 ± 5.0 | 14.6 ± 5.5 | 14.6 ± 5.4 | 14.5 ± 4.9 |
| LBM (kg) | 52.9 ± 5.8 | 53.7 ± 6.0 | 54.6 ± 6.3 a | 55.3 ± 6.4 a b |
| ASMM (kg) | 25.5 ± 3.8 | 26.3 ± 3.6 a | 26.5 ± 3.9 a | 27.2 ± 3.8 a b |
| Non-ASMM (kg) | 27.4 ± 2.4 | 27.4 ± 2.8 | 28.0 ± 2.6 a | 28.1 ± 2.8 a |
| ECW (kg) | 17.9 ± 2.7 | 17.9 ± 2.0 | 18.6 ± 2.7 | 19.5 ± 2.9 a |
| BCM (kg) | 35.0 ± 5.0 | 35.8 ± 4.6 | 36.0 ± 5.7 | 35.8 ± 5.1 |
| REE (kcal/day) | 1513 ± 212 | 1566 ± 188 | 1559 ± 222 | 1600 ± 159 a |
| Fox (mg/min) | 61 ± 28 | 84 ± 41 | 93 ± 21 | 90 ± 32 |
| CHox (mg/min) | 130 ± 75 | 94 ± 87 | 79 ± 80 a | 84 ± 63 |
| IGF1 (nmol/l) | 20 ± 8 | 18 ± 7 | 42 ± 17 a b | 43 ± 18 a |
| T (nmol/l) | 11 ± 5 | 24 ± 8 a | 10 ± 4 a | 22 ± 9 a b |

Significant differences for change within the groups: *P < 0.05 GH vs testosterone, †P < 0.05 GH + testosterone vs testosterone. ^P < 0.05 GH + testosterone vs GH (Mann–Whitney U test), TBF, total body fat; CF, central fat; LBM, lean body mass; ASMM, appendicular skeletal muscle mass; ECW, extracellular water; BCM, body cell mass; REE, resting energy expenditure; Fox, fat oxidation; CHox, carbohydrate oxidation.

*Denotes significant difference (P < 0.05) compared with baseline (Wilcoxon–Signed Ranks test).
**Glucose metabolism**

At baseline, all patients, fasting glucose was < 6.0 mmol/l, but four patients had a 2-h plasma glucose concentration between 7.9 and 11.0 mmol/l (Table 2). Fasting plasma glucose and serum insulin concentrations increased after GH and GH + testosterone but not during testosterone alone. However, no patient recorded a fasting plasma glucose concentration above 6.1 mmol/l at any visit. The 2-h plasma glucose and serum insulin concentrations after the glucose load were increased after GH + testosterone but were not significantly different after GH and testosterone alone (Fig. 3). Two patients recorded a 2-h plasma glucose concentration above 11.1 mmol/l after treatment with GH + testosterone (both of whom had impaired glucose tolerance at baseline) but none after GH or testosterone alone. Of eight patients with normal glucose tolerance at baseline, after each treatment period, two developed impaired glucose tolerance. HOMA-IR increased after GH and GH + testosterone but not after testosterone alone. ISI decreased during GH but not significantly during GH + testosterone or testosterone. IGI did not significantly change with any treatment.

**Lipids**

HDL-cholesterol was significantly decreased after GH but not after GH + testosterone or testosterone (Table 2). TG increased significantly after GH and GH + testosterone but not after testosterone alone. Total- and LDL-cholesterol levels were not affected by the treatments.

**REE and substrate oxidation**

REE was increased after GH + testosterone by 88 ± 96 kcal/day (P = 0.021) but did not significantly change after GH or testosterone alone (Table 1). Fat oxidation increased in all groups, but the change did not quite reach statistical significance. Carbohydrate oxidation decreased after GH but did not significantly change after GH + testosterone and testosterone.

**Side effects**

One patient developed clinically significant peripheral oedema after treatment with GH and GH + testosterone, which resolved after the treatment was discontinued. Inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) and systolic and diastolic blood pressure were not affected by the treatments (data not shown).

**Discussion**

In this study, short-term monotherapy with GH and testosterone increased skeletal muscle mass in men receiving long-term GC treatment. When GH and testosterone were administered in combination, the serum concentration of PIIIP was significantly increased and the increase in skeletal muscle mass was greater than after GH or testosterone alone. These findings suggest that combination treatment with GH and testosterone has great potential to reduce or prevent GC-induced sarcopenia. However, in the doses used, the combination therapy was associated with an increase in post glucose-load glucose concentration of 1.8 mmol/l secondary to a reduction in insulin sensitivity.

GCs have been an important component of therapy in a wide range of medical conditions since they became commercially available in the 1950s. Studies conducted in the United Kingdom in the 1990s reported that 0.5–0.9% of the population were receiving GC.

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**Table 2** Glucose homoeostasis and lipid measurements during treatment with testosterone (T), GH and combination of GH and testosterone in 12 men with long-term exposure of prednisolone. Data is presented as mean ± s.d. or median (25th and 75th percentiles).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Testosterone</th>
<th>GH</th>
<th>GH + testosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose 0 min (mmol/l)</td>
<td>4.6 ± 0.4</td>
<td>4.6 ± 0.4</td>
<td>5.0 ± 0.5<em>a,</em></td>
<td>4.8 ± 0.5*a,t</td>
</tr>
<tr>
<td>Glucose 120 min (mmol/l)</td>
<td>7.1 ± 1.8</td>
<td>7.2 ± 1.7</td>
<td>8.0 ± 2.0</td>
<td>8.9 ± 2.9a</td>
</tr>
<tr>
<td>Glucose AUC (mmol/l×min)</td>
<td>473 ± 99</td>
<td>487 ± 72</td>
<td>524 ± 73</td>
<td>554 ± 60*</td>
</tr>
<tr>
<td>Insulin 0 min (mU/l)</td>
<td>5.2 (3.5–6.8)</td>
<td>4.1 (1.6–6.2)</td>
<td>6.7 (4.8–13.0)a,*</td>
<td>6.9 (4.1–10.6)a,t</td>
</tr>
<tr>
<td>Insulin 120 min (mU/l)</td>
<td>40 (24–52)</td>
<td>34 (28–45)</td>
<td>57 (32–83)</td>
<td>62 (43–85)a</td>
</tr>
<tr>
<td>Insulin AUC (mU/l×min)</td>
<td>2542 (2224–3377)</td>
<td>2159 (1780–2926)</td>
<td>3245 (2037–5001)</td>
<td>3537 (1964–4787)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.1 (0.7–1.4)</td>
<td>0.9 (0.3–1.3)</td>
<td>1.5 (1.2–2.9)*</td>
<td>1.5 (0.8–2.9)*</td>
</tr>
<tr>
<td>ISIcomp</td>
<td>142 (95–196)</td>
<td>158 (123–320)</td>
<td>112 (75–203)*</td>
<td>110 (68–242)</td>
</tr>
<tr>
<td>IGI</td>
<td>12.7 (8.3–19.4)</td>
<td>7.4 (4.2–16.2)</td>
<td>12.5 (9.0–20.2)</td>
<td>14.1 (5.3–15.5)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.0 ± 0.6</td>
<td>5.1 ± 0.8</td>
<td>4.8 ± 0.8</td>
<td>4.9 ± 0.6</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>2.9 ± 0.7</td>
<td>3.0 ± 0.9</td>
<td>2.8 ± 0.8</td>
<td>2.9 ± 0.7</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.7 ± 0.5</td>
<td>1.7 ± 0.4</td>
<td>1.5 ± 0.5*a</td>
<td>1.6 ± 0.5</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>1.0 ± 0.3</td>
<td>1.0 ± 0.3</td>
<td>1.3 ± 0.5<em>a,</em></td>
<td>1.4 ± 0.5*a,t</td>
</tr>
</tbody>
</table>

Significant differences for change within the groups: *P < 0.05 GH vs testosterone, †P < 0.05 GH + testosterone vs testosterone (Mann–Whitney U test); AUC, area under the curve; HOMA-IR, homeostatic model assessment – insulin resistance; ISI, insulin sensitivity index; IGI, insulinogenic index; TG, triglycerides.

*Denotes significant difference (P < 0.05) compared with baseline (Wilcoxon-Signed Ranks test).
Despite the development of effective biologic agents for inflammatory diseases, a recent study reported that rates of GC use are increasing (27). The prevalence of GC use increases with age, with one study reporting that 2.5% of the community aged 70–79 years were receiving GCs (5). As such, GCs are most frequently prescribed to a patient population already at increased risk of sarcopenia.

Sarcopenia in elderly patients is associated with substantial morbidity and increased mortality (6). Therefore, there is a need for therapeutic strategies to prevent or reverse GC-induced protein wasting. Testosterone increases LBM and muscle strength in men on long-term GC treatment (18, 19) and the Endocrine Society has recently recommended testosterone replacement in men with GC-induced hypogonadism (28). However, no standardised therapy is available for the majority of patients, i.e. women and men not fulfilling the criteria for hypogonadism.

High-dose GH has been reported to prevent or reverse GC-induced protein catabolism (14, 15). However, as GCs may induce peripheral insensitivity to IGF1, the minimum effective anabolic dose of GH in this setting is unknown. We recently demonstrated that treatment with GH 0.8 mg/day (approximately two times the physiologic replacement) for 2 weeks reduced whole-body protein oxidation in elderly women receiving chronic GC treatment (16). This study extends those findings by demonstrating that the same GH dose increases lean body and skeletal muscle mass in men after only 2 weeks. As such, GH represents a potential therapeutic option to treat GC-induced sarcopenia.

In our previous study, co-administration of dehydroepiandrosterone did not significantly affect protein metabolism in elderly women on long-term GCs (16). However, in the doses used, testosterone is a much more potent anabolic hormone and co-administration of GH and testosterone produces an additive anabolic effect in hypopituitary and healthy elderly men (10, 13). This study demonstrates that GH and testosterone induced an additive effect on both muscle mass and serum levels of PIIIP in GC-treated men. As such, a combined pharmacologic approach to sarcopenia is likely to represent the best method to maximise favourable body compositional changes and minimise dose-dependent adverse effects in men.

An interesting finding in our study is that testosterone only increased the ASMM component of LBM, while in the two GH arms there were changes in both ASMM and non-ASMM. The cellular mechanisms by which GH and testosterone exert their anabolic actions are not completely understood. Previous studies have reported that GH and testosterone share some, but not other, mechanisms that underlie protein anabolism. In skeletal muscle, GH (29) and testosterone (30) both reduce myostatin, an important endogenous inhibitor of muscle growth. However, while GH consistently increases intramuscular IGF1 mRNA expression (31, 32), the effect of testosterone on skeletal muscle IGF1 mRNA expression is inconsistent and less marked (31, 33). Our study does not provide insight into the mechanisms behind the anabolic action of GH and testosterone. However, it does suggest that GH and testosterone affect skeletal muscle and non-muscle protein differently and therefore must act in part through different mechanisms.

The major concern with the prescription of supraphysiologial doses of GH to patients on long-term GCs is the potential for hyperglycaemia. In our previous study on women on long-term GC therapy, GH 0.8 mg/day increased fasting glucose by 0.5 mmol/l, with no change in post glucose-load glucose concentration (16). In contrast, in this study, GH significantly increased
fasting glucose by 0.4 mmol/l and post glucose-load glucose concentration by 0.8 mmol/l, although the latter result did not reach statistical significance. When GH and testosterone were co-administered the increase in post glucose-load glucose concentration was 1.7 mmol/l and was statistically significant. These findings are particularly salient as patients on long-term GCs have an elevated post glucose-load glucose concentration with no increase in fasting glucose. The apparent increase in sensitivity to the hyperglycaemic sequelae of GH and testosterone in this male cohort is surprising as women in our previous study were more insulin resistant than the men in this study, suggesting a greater underlying risk of hyperglycaemia. Furthermore, the increase in IGF1 concentrations with GH in our previous report in women was 50% greater than the increase in IGF1 in men in the current study. Future studies should assess the effect of lower and individually titrated GH and testosterone doses in men receiving long-term GC treatment to minimise adverse changes in glucose homeostasis.

We were also surprised that the increase in post glucose-load glucose concentration was greatest in the combined treatment group. Testosterone alone did not exert any significant effect on glucose homeostasis. Furthermore, in healthy men, low testosterone concentrations are associated with higher fasting insulin and glucose levels (34). Variable effects of androgen replacement on insulin sensitivity have been reported with an improvement in some studies (35, 36) and no effect in others (37, 38). Our results suggest that co-administration of testosterone is not likely to attenuate the GH-induced deterioration in insulin sensitivity in subjects on long-term GCs.

There are some limitations of this study. The study was not placebo controlled, of short duration and measurements of muscle strength were not included. Furthermore, the short wash-out periods could result in a carryover effect from previous treatment, although this potential limitation may have been mitigated by randomisation of the treatment order. The major limitation is the potential that some of the changes in skeletal muscle mass are secondary to changes in ECW. Previously it has been demonstrated that both short- and long-term administration of GH increases ECW (39, 40). Testosterone also increases ECW, an effect amplified when co-administered with GH (41). Although ECW in our study did not increase after testosterone alone, the change from baseline was only significant after combination with GH and testosterone but not after GH alone. We attempted to account for changes in ECW by using a four compartment model and calculating changes in BCM. Although BCM increased after all three treatment periods, the change did not reach statistical significance. This is probably because of the small sample size and short duration of treatment. However, the changes in PIIIP with GH and testosterone strongly support our conclusion that protein mass was increased and that combined treatment with GH and testosterone exerts the greatest effect. An early increase in PIIIP concentrations has previously been shown to be a good predictor of subsequent increases in ASMM, LBM and muscle strength in elderly men treated with GH and testosterone (42). The additive effect of GH and testosterone on ECW and REE further supports that co-administration of both hormones is more potent than administration of either hormone alone.

In summary, GH treatment at a dose of 0.8 mg/day increases lean body and skeletal muscle mass in men receiving chronic, low-dose GC therapy and its effect is amplified by co-administration of testosterone. We conclude that combination therapy with GH and testosterone has the greatest potential to prevent or reverse GC-induced sarcopaenia in men, using lower GH doses that carry a reduced risk of dose-dependent side effects such as impaired glucose tolerance and consequent diabetes mellitus. This short-term trial is a proof of concept and there is a need for longer and larger studies investigating the effect of combination treatment on muscle function and safety in this patient group.

Declaration of interest
O Ragnarsson and K K Y Ho have received lecture fees from Pfizer. M G Burt is a co-investigator on a study sponsored by Ipsen pharmaceuticals. G Johannsson is consultant for Viropharma and Astra Zeneca and has received lecture fees from Novo Nordisk, Eli Lilly, Merck, Serono, Otsuka and Pfizer.

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