One Year of Growth Hormone Treatment in Adults with Prader-Willi Syndrome Improves Body Composition: Results from a Randomized, Placebo-Controlled Study

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Context: Prader-Willi syndrome (PWS) is a multisymptomatic disease that shares many similarities with the GH deficiency syndrome, including altered body composition with more body fat than lean body mass.

Objective: Our objective was to investigate the effect of GH on body composition in adults with PWS.

Design and patients: Forty-six adults with PWS were randomized to GH or placebo treatment for 12 months in a double-blind trial.

Main Outcome Measures: We evaluated change in regional body composition of the abdomen and thigh as measured by computed tomography and change in total body composition as measured by dual-energy x-ray absorptiometry.

Results: Forty patients completed the study. Baseline median IGF-I score was 0.4. GH treatment increased IGF-I by 125 μg/liter (1.51 SD score), and based upon computed tomography, body composition improved with a decrease in visceral fat mass of 22.9 ml (P = 0.004), abdominal sc fat mass 70.9 ml (P = 0.003), and thigh fat mass 21.3 ml (P = 0.013), whereas thigh muscle mass increased 6.0 ml (P = 0.005). By dual-energy x-ray absorptiometry, lean body mass improved 2.25 kg (P = 0.005), and total fat mass decreased 4.20 kg (P < 0.001). No major side effects were seen.

Conclusion: Unrelated to the GH-IGF-I levels at baseline, our results showed that long-term treatment with GH effectively improved body composition and represents a safe, potential treatment option, relieving some of the negative consequences of PWS. (J Clin Endocrinol Metab 95: 4943–4950, 2010)

Prader-Willi syndrome (PWS) is a rare genetic disorder caused by the lack of paternally expressed genes in the 15q11-q13 region; the incidence is one in 10,000 to one in 15,000 newborns (1, 2). Many features of PWS overlap those of hypothalamic dysfunction, such as hyperphagia, temperature instability, high pain threshold, sleep disorders, hypogonadism, and shorter stature than expected from the genetic potential (1, 2). Reduced GH response to different stimulation tests has been documented in both children and adults (3). Patients with PWS have an abnormal body composition with increased amounts of fat, primarily located sc and to a lesser degree...
viscerally, reduced lean body mass (LBM), and diminished bone mineral density (2, 4–9), all similar to GH deficiency (GHD). The abnormal body composition has been ascribed to impairment of the activity of the GH-IGF system and to hypogonadism (3, 6, 10).

Studies on GH intervention have focused mainly on children, and for more than a decade, children have been treated with GH until late puberty, with improved final height and beneficial effects on body composition. GH has diabetogenic effects, but glucose intolerance has rarely been induced by GH replacement therapy (11, 12).

Recent studies in adult PWS patients have extended the findings in PWS children regarding body composition and metabolic features. So far, observations are few, consisting of small populations (13, 14), inclusion of patients without genetic confirmation of PWS (14), or open-label design (13, 15). Thus, the previous studies in PWS adults need to be confirmed in randomized, larger cohorts and during long-term GH treatment.

In this study, we report the efficacy and safety of GH therapy in genetically verified adults with PWS based on a 12-month placebo-controlled multicenter study.

The primary endpoint was a regional analysis of change in body composition, as measured by computed tomography (CT) of the abdomen and thigh. Secondary endpoints included change in total body composition as estimated by dual-energy x-ray absorptiometry (DXA), bioelectrical impedance, physical performance, glucose metabolism, circulating lipids, and anthropometric measures.

**Patients and Methods**

This report describes results from a 12-month investigator-sponsored double-blind placebo-controlled Scandinavian multicenter study with GH in adults with PWS, conducted between December 2004 and January 2008. The study was performed in accordance with Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). Monitoring of the study was performed by the Good Clinical Practice Unit at Aarhus University Hospital.

**Study population**

Forty-six adults (25 women and 21 men) with genetically verified PWS (methylation positive) were consecutively recruited from the outpatient departments and the national PWS associations in Denmark, Norway, and Sweden. Criteria for inclusion were completed growth of height, age between 16 and 50 yr, no GH treatment for at least 12 months, and no sex-hormone treatment initiated within the last year.

Patients were excluded from the study if they were pregnant or had a major systemic illness including malignancies, untreated respiratory impairment, and uncontrolled or untreated hypertension.

The patients and their caretakers were urged to keep the patient’s diet unchanged during the trial.

**Ethics**

The study was approved by local ethical committees at the University of Oslo, the Karolinska Institute, and the University of Aarhus, and the patients and their guardians consented to study participation before sample collection and examinations.

**Study protocol**

After baseline examination and initiation of study medicine, the patients visited the clinic after 3 and 6 months for monitoring of safety parameters and after 12 months for full examination. The patients were centrally randomized by Novo Nordisk to either placebo or active treatment with GH (Norditropin SimpleXx). In each country, an equal number of patients were randomized to active or placebo treatment. For the initial 4 wk of the study phase, patients were treated with either 0.3 or 0.4 mg/d if body weight was below or above 100 kg, respectively. Thereafter, doses were increased to 0.6 or 0.8 mg/d, respectively, and maintained fixed for the following 11 months. Dosage of GH was based upon experiences from a previous trial with PWS adults (14). Injections were given sc as one dose in the evening by either the patients or their caretakers. The injection procedure was supervised by a caretaker if the patient self-injected. The vials of the trial medicine were returned and counted at the end of the blinded period for monitoring compliance. For safety reasons, levels of total IGF-I were evaluated by two physicians independently of the trial.

**Body composition studies**

The examination of regional body composition (abdominal and thigh) was performed with CT. The patients were scanned at baseline and after 12 months as previously described (16), using comparable 16-slice scanners: in Denmark, Philips MX 8000 (Best, The Netherlands), and in Sweden and Norway, GE LightSpeed pro 16 GE Healthcare, Milwaukee, WI. The basic thin slices, either two or four dependent on the slice thickness, were combined to be used for measurements. In the calculations of volumes, the measurements were standardized to a width of 12 mm. Abdominal scans were made at L2-L3 level, and total abdominal volume, total abdominal fat volume, and visceral abdominal fat volume (VF) were measured. Subcutaneous abdominal fat volume (SF) was calculated by subtracting VF from total abdominal fat volume. Measurements of thigh muscle and fat volumes were made midway between the right greater trochanter and the joint facet of the lateral condyle.

LBM and total fat mass were measured with DXA: in Denmark with Hologic Discovery (Hologic Inc., Waltham, MA), in Sweden with Lunar Prodigy Advance (GE, Madison, WI).

Total body water was calculated and predicted from measurements of bioelectrical impedance.

**Anthropometric methods**

Physical examinations included measurements of height, weight, and waist circumference. Waist circumference was measured as halfway between the costal edge and iliac crest.

**Pulmonary function**

Peak expiratory flow (PEF) was measured three times with a standard analog flow meter using mini-Wright scale values (standard range). The highest value was recorded.
Endocrine and metabolic investigations

Investigations were carried out in the morning with patients in the fasting condition. Free T₄, hemoglobin A1c, insulin, glucose, triglycerides, and total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol were measured locally using routine assays.

A standard 75-g oral glucose tolerance test (OGTT) was performed in the morning in the fasting state. Impaired glucose tolerance and diabetes were diagnosed based upon the 120-min plasma glucose values [from 7.8–11.0 and above 11.1 mmol/liter, respectively, in accordance with the World Health Organization criteria (17)].

Total IGF-I was measured by a time-resolved immunofluorometric in-house assay (18). Inters assay variation was less than 10%, and all samples were measured in the same batch.

Insulin was measured by fluoroimmunoassays (Autodelta insulin; Wallac Oy, Turku, Finland) in Sweden and Denmark, with intra- and interassay coefficients of variation of, respectively, 3.2 and 10.6%, and by RIA (Diagnostic Products Corp., Los Angeles, CA) in Norway. Intra- and interassay coefficients of variation were 9.3 and 10.0%, and by RIA (Diagnostic Products Corp., Los Angeles, CA) in Norway. Intra- and interassay coefficients of variation were 3.2 and 10.6%, and by RIA (Diagnostic Products Corp., Los Angeles, CA) in Norway. Intra- and interassay coefficients of variation were 9.3 and 10.0%, and cross-reactivity with proinsulin was low. Insulin resistance was calculated by the homeostasis model assessment index for insulin resistance (HOMA-IR) as insulin (milliunits per liter) × plasma glucose (millimoles per liter)/22.5 using single fasting samples (19). The threshold for insulin resistance was set at 2.77, as suggested in the Bruneck Study (20).

Physical performance

A quick physical test was performed as previously described (21). The patients walked 10 m two times, and the fastest time was recorded. The 10-m walk was followed by a test where the patients were asked to stand up from a sitting position and sit down again as fast as possible either five or 10 times. The time was recorded and converted into a score from 0–4.

Statistical analyses

Similarity calculation at baseline was made by either Student’s t test or Wilcoxon signed rank test depending on whether the data were normally distributed or not.

Calculations of differences (12-month value − baseline value) were performed by ANOVA, with the baseline values used as covariates. The last observation was carried forward for missing data or dropouts in the study. Our cohort represents a part of the total population of adults with PWS in Scandinavia, for whom information of the mean value for the parameters evaluated in the present study does not exist. Therefore, the estimated means (mean values from our cohort) and 95% confidence intervals were calculated. Statistical significance was set at P < 0.05.

The statistical analysis with ANOVA was performed with SAS version 9.2 (SAS Institute Inc., Cary, NC). All other analyses were performed with Stata/IC 10.1 (StataCorp LP, College Station, TX).

Results

Baseline characteristics of the cohort (Table 1)

Baseline data for the entire cohort has previously been described (16). Peak GH response was examined by a standard GHRH-arginine test, six patients fulfilled body mass index (BMI)-related cutoff limits for GHD. At baseline examination, three patients had diabetes mellitus (DM), and additionally, four patients had DM as diagnosed by OGTT. Ten patients had an impaired OGTT, and 29 had a normal OGTT. Nine men and seven women received sex-steroid replacement. Two women were treated for primary hypothyroidism. Baseline characteristics of patients randomized to GH or placebo treatment are shown in Table 1. No differences between the groups were observed.

<table>
<thead>
<tr>
<th>Number</th>
<th>Placebo</th>
<th>GH</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>28.9 ± 6.8</td>
<td>28.6 ± 6.7</td>
<td>0.88</td>
</tr>
<tr>
<td>BMI (kg/m²)$</td>
<td>27.0 (19.8–40.1)</td>
<td>27.8 (20.4–43.6)</td>
<td>0.52</td>
</tr>
<tr>
<td>IGF-I SDS</td>
<td>−0.05 ± 1.65</td>
<td>−0.25 ± 1.41</td>
<td>0.66</td>
</tr>
<tr>
<td>Vf (ml)$</td>
<td>88 (31–187)</td>
<td>82 (29–169)</td>
<td>0.90</td>
</tr>
<tr>
<td>SF (ml)</td>
<td>410 ± 243</td>
<td>427 ± 224</td>
<td>0.82</td>
</tr>
<tr>
<td>Thigh fat (ml)</td>
<td>178 ± 80</td>
<td>176 ± 83</td>
<td>0.91</td>
</tr>
<tr>
<td>Thigh muscle (ml)</td>
<td>105 ± 33</td>
<td>109 ± 28</td>
<td>0.69</td>
</tr>
<tr>
<td>DXA lean body mass (kg)</td>
<td>40.2 ± 7.1</td>
<td>39.8 ± 8.8</td>
<td>0.87</td>
</tr>
<tr>
<td>DXA fat mass (kg)</td>
<td>30.7 ± 13.8</td>
<td>31.6 ± 13.3</td>
<td>0.93</td>
</tr>
<tr>
<td>Total body water (liters)</td>
<td>36.0 ± 6.9</td>
<td>36.7 ± 8.6</td>
<td>0.77</td>
</tr>
<tr>
<td>Total cholesterol (mmol/liter)</td>
<td>4.70 ± 0.83</td>
<td>4.53 ± 0.67</td>
<td>0.47</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/liter)</td>
<td>1.38 ± 0.38</td>
<td>1.44 ± 0.45</td>
<td>0.65</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/liter)</td>
<td>3.06 ± 0.81</td>
<td>2.74 ± 0.64</td>
<td>0.16</td>
</tr>
<tr>
<td>Triglyceride (mmol/liter)$</td>
<td>0.73 (0.40–1.52)</td>
<td>0.84 (0.44–1.95)</td>
<td>0.30</td>
</tr>
<tr>
<td>Insulin (pmol/liter)</td>
<td>30.0 ± 20</td>
<td>35.5 ± 62</td>
<td>0.19</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.054 ± 0.004</td>
<td>0.056 ± 0.009</td>
<td>0.36</td>
</tr>
<tr>
<td>HOMA-IR$</td>
<td>0.94 (0.27–3.26)</td>
<td>1.10 (0.42–3.21)</td>
<td>0.16</td>
</tr>
<tr>
<td>Fasting glucose (mmol/liter)</td>
<td>4.74 ± 0.74</td>
<td>5.28 ± 1.45</td>
<td>0.12</td>
</tr>
<tr>
<td>PEF (liters/min)</td>
<td>274 ± 92</td>
<td>268 ± 80</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Results are shown as mean ± sd or mean (range). P values were calculated by t test. Results marked by $ are shown as median values (10th; 90th percentile). P values were calculated by rank sum. HbA1c, Hemoglobin A1c.
Compliance

Only a few deviations of adherence to the protocol were recorded. In total, six of 46 patients did not complete the study. In the GH-treated group, three patients were withdrawn by the investigator within the first 6 months: one severely obese patient (BMI 64 kg/m²) due to progression of already known DM, one patient due to lack of compliance, and one patient who had never started with the trial medicine. In the placebo group, two patients left the study due to complaints of side effects (increased weight and feeling depressed), and one left the study for unknown reasons.

Furthermore, two patients erroneously continued with the initial dose of trial medicine for 6 months instead of 4 wk, one patient overdosed study medication for the first 5 months after which the patient was without treatment for 1 month, and finally, one patient was without treatment for a few days.

Otherwise, counting of the empty vials did not reveal any significant lack of compliance, and no patients were withdrawn from the study due to inappropriately high IGF-I levels.

Body composition measurements (Table 2)

CT measurements (Fig. 1, A and B)

The VF and SF decreased in the GH group vs. the placebo group with 22.9 ml (−38.1 to −7.8 ml; P = 0.004) and 70.7 ml (−115 to −26.3; P = 0.003), respectively (Fig. 2).

A reduction in thigh adipose tissue and an increase in thigh muscle was seen in the GH group vs. the placebo group: 21.3 ml (−38.0 to −4.7 ml; P = 0.013) and 6.1 ml (1.9–10.2; P = 0.005), respectively (Fig. 3).

A gender difference in VF was found, because VF in women remained unchanged (P = 0.15), whereas VF in men decreased (P = 0.04). No other gender differences were observed.

DXA measurements (Fig. 1C)

LBM increased 2.25 kg (0.725–3.77 kg; P = 0.005), whereas a reduction in fat mass of 4.20 kg (−6.40 to −2.00; P < 0.001) in the GH group vs. the placebo group was seen.

Bioimpedance

Total body water showed an insignificant increase of 1.15 liters (−0.11–2.40 liters; P = 0.07) in the GH group vs. the placebo group.

Laboratory, anthropometric measurements, and PEF (Table 3)

The IGF-I level increased in the GH-treated group vs. the placebo group by 125 μg/liter (84–167 μg/liter; P < 0.001), equal to 1.51 sd score (SDS) (0.95–2.07 SDS; P < 0.001).

LDL cholesterol decreased in the GH vs. the placebo group by 0.27 mmol/liter (−0.53–0.00 mmol/liter; P = 0.047), whereas no changes were found in total and HDL cholesterol or triglycerides.

No changes in fasting glucose or fasting insulin were found in either the GH- or the placebo-treated group. OGGTT in the GH group at the end of the treatment period revealed three patients with DM, 10 patients with impaired glucose tolerance, and eight patients with a normal test. The corresponding values in the placebo group were 2, 6, and 11; the differences were not statistically significant. No difference in HOMA-IR was found. However, in one patient in the GH group and one patient in the placebo group, the value had increased above 2.77.

No changes were seen in BMI, waist circumference, or PEF.

Physical performance

In the 10-m walk test, six patients in the GH group walked faster and 12 patients slower. In the placebo group, two patients walked faster and 14 patients walked slower, the reminder either did not perform the test or showed an unchanged performance. The repeated rising from a chair test scores were unchanged. However, six patients in the GH group had poorer scores at 12 months compared with baseline, whereas in the placebo group, four patients had worse scores and two had a better score.

Adverse effects

As mentioned in the compliance section, six patients left the study before the study ended.

| TABLE 2. Change in estimated mean and 95% confidence interval (CI) of the estimate in body composition in PWS during 12 months of GH treatment |
|-----------------|--------|--------|-----------------|-----------------|-----------------|
|                  | n     | Placebo | GH   | Estimate (95% CI) | P valuea         |
| VF (ml)          | 41    | 15.6    | −7.4 | −22.9 (−38.1 to −7.8) | 0.004           |
| SF (ml)          | 41    | 38.6    | −32.6| −70.7 (−115.0 to −26.3) | 0.003           |
| Thigh fat (ml)   | 41    | 15.6    | −5.7 | −21.3 (−38.0 to −4.7)  | 0.013           |
| Thigh muscle (ml)| 41    | −0.1    | 6.0  | 6.1 (1.9–10.2)         | 0.005           |
| DXA lean body mass (kg) | 44 | 0.01   | 2.26 | 2.25 (0.72–3.77)    | 0.005           |
| DXA fat mass (kg) | 44    | 2.24    | −1.96| −4.20 (−6.40 to −2.00) | <0.001          |
| Total body water (liters) | 44 | 0.05  | 1.20 | 1.15 (−0.11–2.40) | 0.07            |

a ANOVA.
One patient with manifest diabetes at enrollment was withdrawn due to uncontrolled diabetes after initiation of GH. OGTT at the end of the study revealed that seven patients in the GH group with a normal baseline OGTT had impaired glucose tolerance, and nobody had developed DM. The corresponding values in the placebo group were two and one. One patient (GH group) described a few isolated instances of headache and nausea within 2 months of treatment.

Mild progression of pretibial edema was reported in seven patients treated with GH and in five treated with placebo. On the other hand, five patients in the GH group were reported to have less pretibial edema after 1 yr compared with baseline. In the placebo group, four patients had progression of preexisting pretibial edema.

Total body water did not change; however, there was a tendency toward an increase ($P = 0.07$).

No other side effects were seen.

**FIG. 1.** A and B, Mean change ($\pm$ ss) in abdominal visceral and sc fat and in mid thigh fat and muscle as measured by CT; C, mean change ($\pm$ ss) in LBM and total fat mass as measured by DXA (black bars, GH-treated patients; white bars, placebo-treated patients).

**FIG. 2.** CT scans of abdomen at L2 level of a male PWS patient at enrollment (left) and after 1 yr of GH therapy (right), illustrating reduced amount of sc and visceral fat.
**Discussion**

This is the first large-scale and long-term double-blind placebo-controlled trial with GH in adults with PWS. Beneficial effects were seen in the GH-treated group. Regional measurement of body composition showed improvement in both sc and visceral fat as well as in thigh muscle as measured by CT. The results in measurement of whole-body composition measured with DXA scan showed similar beneficial results. Thus, body fat decreased, and LBM increased. LDL cholesterol decreased, and no significant changes were observed in glucose levels or glucose tolerance.

We found a reduction in estimated mean VF of nearly 25% in the GH-treated group vs. the placebo group when comparing with the baseline level of VF. A high amount of visceral fat is associated with metabolic consequences (22). However, adults with PWS have relatively less visceral fat compared with simple obesity (4, 5, 16), whether the effect on visceral fat will result in a favorable impact on metabolic complications needs additional observation for many more years to be answered. The gender difference in VF was unexpected and has not previously been reported in this specific group of patients. We found no differences in GH dosage, IGF-I, or waist circumference that could explain the difference. VF in GHD women is expected to decrease during GH therapy (23).

The reduction on sc fat was as impressive as VF; the estimated mean reduction of SF reduction compared with baseline value was nearly 20%, whereas the reduction on thigh fat was more modest, estimated at 12%. Similar reduction in VF was found in an open-labeled study by Marzullo et al. (24) on adults with PWS, whereas the reduction in SF was less pronounced.

We found a small but significant increase of thigh muscle volume of approximately 6%. Whether this increase reflects increased hydration of the muscle fibers remains unknown, but total body water did not increase significantly. Patients with PWS have decreased muscular tone and muscular mass (2, 4, 16, 25), resulting in reduced physical performance, and our finding of increased muscle volume is in accordance with the improved exercise capacity in GH-treated adults with PWS described by Gonzoni et al. (13).

The estimated mean of LBM increased 2.25 kg, and the corresponding reduction in fat mass was 4.20 kg, both in line with previous studies on GH intervention in adults with PWS (13–15) and in adults with severe GHD (26).

The majority of the patients in our cohort were living in special group homes for PWS adults with extensive control of calorie intake and exercise. As a consequence, BMI was lower than what has previously been described (5, 7, 9, 13–15, 25). Using BMI-related cutoff limits for diagnosis of GHD, only six patients in our cohort fulfilled the established criteria for profound GHD (16). Additionally, the calculated differences in the GH group were unrelated

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**TABLE 3.** Change in estimated mean and 95% confidence interval (CI) for the estimate in metabolic, anthropometric, and PEF measurements in PWS during 12 months of GH treatment

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Placebo</th>
<th>Active</th>
<th>Estimate (95% CI)</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total IGF-I (μg/liter)</td>
<td>45</td>
<td>3</td>
<td>128</td>
<td>125 (84–167)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/liter)</td>
<td>44</td>
<td>0.33</td>
<td>0.07</td>
<td>−0.26 (−0.54–0.03)</td>
<td>0.07</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/liter)</td>
<td>44</td>
<td>−0.01</td>
<td>−0.03</td>
<td>0.02 (−0.12–0.16)</td>
<td>0.79</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/liter)</td>
<td>42</td>
<td>0.31</td>
<td>0.05</td>
<td>−0.27 (−0.53 to −0.01)</td>
<td>0.047</td>
</tr>
<tr>
<td>Triglyceride (mmol/liter)</td>
<td>44</td>
<td>−0.13</td>
<td>−0.02</td>
<td>0.10 (−0.18–0.39)</td>
<td>0.45</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>46</td>
<td>0.001</td>
<td>0.003</td>
<td>0.001 (−0.001–0.004)</td>
<td>0.37</td>
</tr>
<tr>
<td>Fasting glucose (mmol/liter)</td>
<td>45</td>
<td>0.48</td>
<td>0.70</td>
<td>0.22 (−0.93–1.37)</td>
<td>0.70</td>
</tr>
<tr>
<td>Fasting insulin (pmol/liter)</td>
<td>43</td>
<td>4.5</td>
<td>−3.7</td>
<td>−8.2 (−19.0–2.6)</td>
<td>0.13</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>43</td>
<td>0.27</td>
<td>−0.10</td>
<td>−0.37 (−0.15–0.90)</td>
<td>0.16</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>44</td>
<td>2.1</td>
<td>0.4</td>
<td>−1.7 (−5.2–1.7)</td>
<td>0.31</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>45</td>
<td>0.76</td>
<td>0.15</td>
<td>−0.61 (−1.69–0.46)</td>
<td>0.26</td>
</tr>
<tr>
<td>PEF (liters/min)</td>
<td>40</td>
<td>6</td>
<td>15</td>
<td>10 (−13–32)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

HbA1c, hemoglobin A1c.

a ANOVA.
to both the GHRH-arginine peak values and the baseline total IGF-I values (data not shown). Despite this, the improvement in body composition strongly supports the concept that adults with PWS have a functional GHD.

A small reduction in LDL cholesterol was found. This is a new finding because none of the previous GH intervention studies have reported this (14, 15, 24). However, despite the fact that PWS patients in most studies are obese, hypercholesterolemia does not seem to be frequent in the PWS group, probably related to the smaller amount of visceral fat. Some studies on GH replacement in GHD adults have reported similar potentially beneficial effects upon circulating lipids (27, 28).

No changes were found in physical performance, which is somewhat surprising because many patients and caretakers reported that the patients, subsequently shown to have received active treatment, had more energy and in general performed better in their normal physical activity. The test we used was planned to be easy and fast to carry out for the patients. However, for several of the patients in this study, the test was performed without difficulties (not strenuous enough), and the baseline results left no or little room for improvement. We did not encourage the patients to change their level of physical activity; hence, we did not consider any possible effects of training in the treatment groups. The lack of improvement in physical performance is a limitation of the present study. However, using a more intensive protocol, Gondoni et al. (13) showed an improvement in exercise capacity in PWS adults with GH treatment in an open design, providing evidence that effects of GH on physical activity can be measured with the right test.

Because GH has a diabetogenic effect, glucose was monitored closely, but we saw no significant changes in glucose metabolism. At baseline, three patients were treated for diabetes, and besides the patient withdrawn from the study, only one patient in the GH group had increased HOMA-IR after 1 yr compared with baseline. Based on our results and the three previous interventions studies (13–15), glucose metabolism was not significantly affected by GH treatment, and it seems safe to treat with GH in this respect.

A few patients developed mild edema. However, this occurred in both treatment groups, and in most of the patients, the edema was considered to be of no clinical importance, and GH dosage was not reduced. No patients developed severe edema during GH treatment. Increase in total body water will be expected with GH treatment, indirectly indicating adequate GH doses; in this study the increase was non-significant.

Apart from the six patients who left the study, compliance was good. The trial medicine was well tolerated, and most patients self-injected the medicine without any major problems being reported.

In conclusion, 12 months of GH therapy improved body composition. Both regional and total fat mass was reduced, whereas regional muscle mass and total LBM increased. No major side effects were seen, and glucose metabolism was not affected. Based on these positive effects on body composition, we consider GH treatment a logical treatment possibility in adults with PWS.

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