Endocrine (2012) 41:191–199
DOI 10.1007/s12020-011-9560-4

REVIEW

Growth hormone treatment in adults with Prader-Willi syndrome: the Scandinavian study

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Received: 1 October 2011 / Accepted: 29 October 2011 / Published online: 12 November 2011

Abstract Prader-Willi syndrome (PWS) is characterized by short stature, muscular hypotonia, cognitive dysfunction, and hyperphagia usually leading to severe obesity. Patients with PWS share similarities with growth hormone deficiency (GHD). Few studies have dealt with growth hormone (GH) treatment in PWS adults. The purpose of the Scandinavian study was to evaluate the effects of GH on body composition, lipid and glucose metabolism, physical performance and safety parameters in adults with PWS. Twenty-five women and 21 men with PWS were randomized to treatment with GH or placebo during 1 year followed by 2 years of open labeled GH treatment. At baseline 1/3 had normal BMI, six patients severe GHD, ten impaired glucose tolerance and seven diabetes. At 1 year insulin-like growth factor I (IGF-I) SDS had increased by 1.51 ($P < 0.001$) and body composition improved in the GH treated group. Visceral fat decreased by 22.9 ml ($P = 0.004$), abdominal subcutaneous fat by 70.9 ml ($P = 0.003$) and thigh fat by 21.3 ml ($P = 0.013$), whereas thigh muscle increased 6.0 ml ($P = 0.005$). Lean body mass increased 2.25 kg ($P = 0.005$), and total fat mass decreased 4.20 kg ($P < 0.001$). The positive effects on body composition were maintained after 2 years of GH treatment. Peak expiratory flow increased by 12% ($P < 0.001$) at 2 years of GH treatment. Lipid and glucose metabolism were unchanged, however, three patients developed diabetes at 2 years of GH treatment. In conclusion GH treatment had beneficial effects on the abnormal body composition without serious adverse events making it a logic treatment option in adults with PWS.

Keywords PWS · GH · Body composition

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Introduction

The clinical features of Prader-Willi syndrome (PWS) was first described 1956 by Prader et al. [1]. PWS is a rare disease affecting ~1 in 15 000 newborns, equally frequent in both genders [2, 3]. PWS is characterized by several symptoms and signs [4, 5]. Typical dysmorphic features include a long narrow face, narrow bifrontal diameter, almond-shaped eyes, small mouth with a thin upper lip, small hands and feet for height and age, and narrow hands with a straight ulnar border [4, 5]. The clinical features of PWS vary with age. In the neonatal phase severe muscular hypotonia, a weak cry and a poor sucking reflex are typical features. During infancy muscular hypotonia improves, but a mild to moderate intellectual dysfunction and delayed psychomotor development become increasingly apparent

along with impaired skeletal growth. From the age of 2–4 years hyperphagia becomes frequent and obesity develops if constant vigilance of a strict diet and scheduled daily physical activities are not established. Puberty is delayed or incomplete with a decreased or absent growth spurt, resulting in reduced final adult height in both genders [6]. Most patients with PWS are hypogonadal, which traditionally has been considered of hypothalamic origin [2]. However, recent studies have pointed at a peripheral etiology to the hypogonadism as most common [7, 8]. The fertility in PWS is not known in detail, but pregnancy in three PWS women has been reported [9, 10]. Psychiatric and behavioral problems become more prominent with increasing age, and are together with the patients hyperphagia, and cognitive impairments the main hindrances to independent living for the PWS adults. Most live either with parents or in specialized homes/institutions and manage to have sheltered work.

Early death, as early as in the third decade of age, has been reported previously due to obesity related problems such as DM type 2, dyslipidaemia, cardiovascular disease, and pulmonary dysfunction [11] but a significant number of PWS patients has died suddenly for unknown reasons. Today, PWS is diagnosed in early childhood, increasing the possibilities for early intervention, and hopefully a future reduction in health problems and mortality.

Diagnosis

During more than two decades PWS was diagnosed based on clinical findings only. The clinical diagnosis is difficult which led to the formulation of diagnostic criteria Holm et al. 1993 [5]. Today the diagnosis of PWS is made according to results of genetic analysis identifying an absent paternal expression of the q11–q13 region of chromosome 15 in ~70% caused by deletion, in 25–30% by maternal uniparental disomy (UPD) and in a few imprinting center defects or balanced translocations [12]. The most common used genetic analysis is the PW71 methylation-test [12] which however does not identify the underlying specific genetic defect. Several different genes in the chromosome 15q11–13 region have been identified [12]. The clinical implications of these genes are not completely known but impairments in metabolism and brain development are assumed.

GH in children with PWS

Treatment with growth hormone (GH) in children with PWS has been used in routine clinical practice for almost two decades, and several reports have been published since the late 1990s demonstrating normalization of height standard deviation score (SDS) and improvement in body composition [2, 13–16]. In a 4-year follow-up study, the positive effects on body composition were maintained and a positive effect on bone mass density was found [13]. One of the studies reported improved physical performance, as monitored by physical tests and inspiratory/expiratory muscle strength [16]. In a randomized 1-year study of infants and toddlers, positive effects in both mental and motor development were described [17], suggesting that early introduction of GH in PWS children might be beneficial for the children on a long-term basis. So far, GH treatment has been continued until final adult height has been reached, after which the treatment has been discontinued and a new evaluation of GH secretion performed.

GH in adults with PWS

Adults with PWS share similarities with GH deficient patients (GHD) as regards body composition with reduced lean body mass (LBM) (compared to both healthy normal-weight and obese individuals) and increased fat mass (FM) [18]. GH treatment in non-PWS GHD adults improves body composition and has beneficial effects on muscle strength and physical performance [19]. Thus, GH treatment could be beneficial in adult PWS patients.

Prior to the initiation the Scandinavian trial, only one study evaluating the effects of GH treatment in adults with PWS had been published [18]. That study, the Karolinska trial [18], reported of improved body composition with reduction in total FM, increased LBM, and positive effects on cognitive parameters such as mental speed and flexibility and motor performance [18].

The overall aims of the Scandinavian study were to evaluate the effects of GH treatment on body composition, lipid and glucose metabolism and physical fitness and safety aspects of the treatment.

Materials and methods

Patients and study design

Forty-six adults (25 women and 21 men) with genetically verified PWS were consecutively recruited from the national PWS associations and outpatients departments in Sweden, Norway, and Denmark. The patients and their caretakers were encouraged to maintain the patient's diet unchanged during the trial.

After enrollment and baseline characterization the patients were randomized to treatment with GH or placebo for 12 month in a double blind trial followed by a 2 years open label GH treatment period. Thirty-nine patients completed the 3 years study. Data from computed tomography (CT) of the abdomen in 22 healthy controls, 11

women and 11 men; median age 30 years, range 19–45 years; median BMI 29 kg/m^2, range 21–37 kg/m^2, was included for comparison of baseline data.

Body composition

Body composition was examined at baseline and at 12, 24, and 36 months with CT, dual energy X-ray absorptiometry (DXA) and bioelectrical impedance (BIA).

The examination of regional body composition (abdominal and thigh) was performed with CT as previously described [20] using comparable 16 slice scanners. CT measurements were all evaluated at a Philips Extended Brilliance™ Workspace; Version v 7.1. The basic thin slices, either two or four dependent on the slice thickness, were combined for measurements. In the calculations of volumes the measurements were standardized to a width of 12 mm. Abdominal scans were made at the 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. Visceral to subcutaneous fat ratio (VS) was calculated as VF divided by SF, subcutaneous fat fraction (SFF) was calculated as SF divided by total abdominal volume, and visceral fat fraction (VFF) as VF divided by total abdominal volume. Thigh muscle and fat volumes were measured midway between the right greater trochanter and the joint facet of the lateral condyle as earlier described [21].

LBM and total FM were measured with comparable DXA scanners and total body water (TBW), was calculated from measurements of BIA.

Laboratory assessments

Stimulation of GH secretion was performed at study initiation only. All other laboratory assessments and tests were performed every 6 months.

Growth hormone stimulation test

After inclusion the GH stimulation test was performed with a bolus injection of GH releasing hormone (GHRH) (1 μg/kg) followed by an infusion of arginine (0.5 g/kg, maximally 35 g) during 30 min. GH was measured every 10 min, and the GH peak was recorded [22]. The cut-off levels for GHD was 11.5 μg/l for normal body weight, 8.0 μg/l for overweight, and 4.2 μg/l for obese [23]. GH was determined by flouroimmunoassays (Delfia hGH Wallac Oy, Turku, Finland) in Sweden and Denmark, and by radio immunoassays (Orion Diagnostica, Espoo, Finland) in Norway.

Oral glucose tolerance test

A standard 75 g oral glucose tolerance test (OGTT) was performed in the morning in the fasting state. Impaired glucose tolerance and diabetes was diagnosed based upon the 120 min plasma glucose values (between 7.8 and 11.0 and above 11.1 mmol/l, respectively, in accordance with the WHO criteria [24].

Assays

Serum TSH, LH, FSH, testosterone, estradiol, HbA1c, triglycerides and total, low (LDL) and high (HDL) density lipoprotein cholesterol were measured in the fasting state according to standard local procedures. Total insulin like growth factor I (IGF-I) was analyzed centrally with a time-resolved immunofluorometric in-house assay [25].

Total cholesterol >5.0 mmol/l, LDL >3.0 mmol/l, HDL <1.2 mmol/l for women and <1.0 mmol/l for men and triglycerides >1.7 mmol/l were considered abnormal.

Insulin was measured by flouroimmunoassays (Insulin Autodelfia® Perkin Elmer Life Sciences, Turku, Finland) in Sweden and Denmark and by radio immunoassay (DPC, Los Angeles, CA, USA) in Norway. Cross reactivity with proinsulin was low. Insulin resistance was calculated by the homeostasis model assessment index (HOMA-IR) as insulin(mU/l)*plasma glucose(mmol/l)/22.5 using single fasting samples [26]. The threshold for insulin resistance was set at 2.77 [27].

Anthropometric methods

Physical examination included measurements of height, weight, waist, and hip. Waist and hip were measured in standing position. Waist circumference was measured halfway between the costal edge and iliac crest and cutoff points for obesity were set to 88 cm in women and 102 cm in men. Hip was measured at the greatest circumference and waist-to-hip (WH) ratio above 0.85 in women and 1.0 in men defined obesity. Body mass index (BMI) was calculated as weight divided by the square height, kg/m^2. BMI from 18.5 to 25 kg/m^2 was defined as normal, between 25 and 30 kg/m^2 as overweight and above 30 kg/m^2 as obese according to WHO criteria.

Pulmonary function

Peak expiratory flow (PEF) was measured three times with a standard analogue flow-meter using Mini-Wright scale values (Standard range). The highest value was recorded.

Assessment of physical function

Testing of lower-extremity function ad modum, Guralnik [28] was used to examine the patient's standing balance, walking speed, and ability to rise from a chair.

In the original study by Guralnik et al. [28] a 2.4 m walk was timed. Most of our patients managed the 2.4 m walking distance without problems. Therefore, the test was extended to 10 m.

Statistics

Statistical significance was set at $P < 0.05$ in all calculations.

Data are presented as median (10th and 90th percentile) unless otherwise stated. Comparisons between groups were made by either Students *T* test, Mann–Whitney rank sum test or Wilcoxon signed rank test depending on whether the data were normally distributed or not. Relationships were analysed with either Spearman correlations, Wilcoxon matched pairs signed rank test or Wilcoxon signed rank test. Calculations of differences (12 months value − baseline value) were performed by ANOVA and calculations on differences after two (24 months value − value at inclusion) years of GH were performed by paired *t* test.

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

Results

GH and IGF-I

The GHRH-arginine stimulation test for GH secretion was performed in 41 patients. The GH responses were very heterogeneous, ranging from severe GHD to a peak response higher than 70 μg/l [29] (median response 16.7 μg/l (5.95–44.55 μg/l). Six patients fulfilled the BMI related cut-off limits for severe GHD. Two of these patients had normal BMI, two were overweight and two were obese.

The baseline IGF-I SDS did not differ between the group of patients randomised to GH treatment and placebo ($P = 0.66$) [30]. During 1 year of GH treatment IGF-I levels increased in the GH treated group by 125 μg/l (84–167 μg/l; $P < 0.001$), equal to 1.51 SDS (0.95–2.07 SDS; $P < 0.001$) and at 2 years follow-up IGF-I had increased by 58 μg/l (45–72 μg/l; $P < 0.001$) [31].

Body composition

At baseline median BMI was 27.2 kg/m^2 (19.9–40.9 kg/m^2), 17 had normal BMI (6 women and 11 men), 12 were overweight (7 women and 5 men), and 17 were obese (12 women and 5 men).

Comparing values from CT examinations obtained at baseline in PWS adults ($n = 44$) to values from control subjects ($n = 22$) median SF were 371 ml and 162 ml ($P = 0.02$), median VF 88 ml and 124 ml ($P = 0.11$), median VS 0.24 and 0.65 ($P = 0.001$) [29]. The median SFF was higher than VFF (0.53 vs 0.12, $P < 0.001$). No significant differences in the results of the abdominal examinations between men and women were found [29]. The increased subcutaneous fat could also be demonstrated peripherally with a median thigh fat volume of 179 ml and thigh muscle volume of 104 ml [29].

During the placebo-controlled period no changes were found in BMI or anthropometrics in response to GH treatment [30]. VF and SF decreased in the GH treated 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 [30]. A reduction in thigh adipose tissue and an increase in thigh muscle were seen in the GH treated group; 21.3 ml (−38.0–4.7 ml; $P = 0.013$) and 6.0 ml (1.9–10.2; $P = 0.005$), respectively. A gender difference in VF was found, since VF in women remained unchanged ($P = 0.15$), whereas VF in men decreased ($P = 0.04$). No other gender differences were observed. DXA measurements demonstrated an increase in LBM of 2.25 kg (0.725–3.77 kg; $P = 0.005$), and a reduction in FM of 4.20 kg (−6.40 to −2.00 kg; $P < 0.001$) in the GH treated group (Fig. 1). BIA showed an insignificant

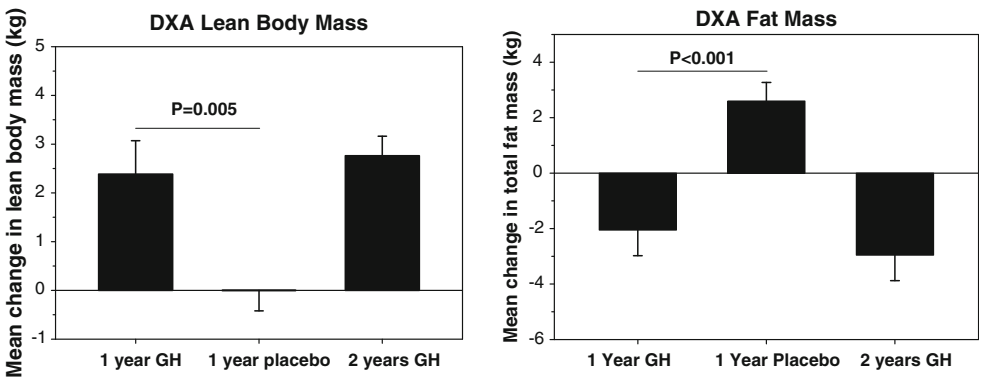

Fig. 1 Change in lean body mass and fat mass by DXA at one and 2 years of GH treatment

increase in TBW of 1.15 l (−0.11–2.40 l; $P = 0.07$) in the GH treated group [30].

At 2 years of GH treatment a reduction in SF by 53.3 ml (13.8–92.9 ml; $P = 0.01$), and in VF by 7.2 ml (−3.6–18.0 ml; $P = 0.18$) were found [31]. Thigh muscle increased by 6.7 ml (3.7–9.7 ml; $P < 0.001$), and a tendency to a reduction in thigh fat 12.8 ml (−1.5–27.1 ml; $P = 0.08$) was observed. DXA measurements showed an increase in LBM of 2.8 kg (1.9–3.6 kg; $P < 0.001$), whereas total FM decreased by 3.0 kg (1.1–4.8 kg; $P = 0.003$) (Fig. 1). TBW increased by 2.1 L (1.1–3.1 L; $P < 0.001$ [31]. No changes were found in BMI or anthropometrics.

Glucose and lipid metabolism (Tables 1, 2)

At baseline 29 patients had normal OGTT, whereas 10 (5 women and 5 men) had an impaired glucose tolerance (IGT). Seven had diabetes (all women) of whom three were already diagnosed with diabetes before inclusion in the study (two with diabetes type 2 and one with diabetes type 1). When evaluating insulin sensitivity by means of the HOMA-index only four patients had an index >2.77, two of whom had known diabetes. Three diabetic patients had HbA1c above normal [29].

In the placebo-controlled treatment trial no overall changes in fasting glucose, fasting insulin or HOMA-IR were found in either group [31]. Eight patients in the GH treated group had a normal glucose tolerance, ten patients had IGT and three patients had DM. The corresponding values in the placebo treated group were 11, 6, and 2—the differences not being statistically significant.

Overall, no changes in fasting glucose, fasting insulin, or insulin sensitivity after 2 years of GH therapy were observed. However, a small increase in HbA1c of 0.2% (0.0–0.3%; $P = 0.01$) was seen [31]. Among the 39 patients who completed the 2 years of GH treatment 24 had a normal glucose tolerance (NGT) at baseline, while eleven had IGT and four had DM. At 2 years of GH treatment, five patients with NGT developed IGT and another three patients with initial IGT progressed to DM. By contrast, three patients with IGT normalized glucose tolerance during treatment [31].

At baseline median total LDL- and HDL-cholesterol, as well as triglycerides were all within the normal range. In 10 patients total cholesterol was above 5 mmol/l, and in 14 LDL-cholesterol was above 3.0 mmol/l, with the highest value being 4.7 mmol/l. In four men and four women HDL-cholesterol levels were below the cut-off limit and three patients had triglycerides above 1.7 mmol/l. No gender differences were seen [29].

LDL-cholesterol decreased in the GH treated vs the placebo treated group by 0.27 mmol/l (−0.53 to −0.00 mmol/l; $P = 0.047$) whereas no changes were found in total and HDL-cholesterol or triglycerides [30]. No changes in circulating lipids were observed during 2 years follow-up of GH treatment [31].

Assessment of physical function

During GH treatment no significant effects were found on the Guralnik test battery [30, 31]. No differences in

Table 2 Results of oral glucose tolerance test (number of patients) at baseline and after two years of GH therapy in 39 patients with Prader-Willi syndrome

Baseline	*N*	2 years GH	*N*
Normal	24	Normal	19
		Impaired	5
		DM	0
Impaired	11	Normal	3
		Impaired	5
		DM	3
DM	4	Normal	0
		Impaired	0
		DM	4

DM Diabetes mellitus

Table 1 Baseline laboratorial characteristics of 46 adults with Prader-Willi syndrome

	N	Median (10th–90th percentile)	Normal range
Cholesterol (mmol/l)	45	4.50 (3.76–5.66)	<5.0
LDL-cholesterol (mmol/l)	43	2.90 (2.00–4.02)	<3.0
HDL-cholesterol, men (mmol/l)	21	1.20 (0.82–2.08)	>1.0
HDL-cholesterol, women (mmol/l)	24	1.40 (0.90–1.45)	>1.2
Triglycerides (mmol/l)	45	0.75 (0.41–1.70)	<1.7
HbA1c (%)	44	0.054 (0.048–0.060)	0.051–0.062
Fasting glucose (mmol/l)	46	4.9 (3.9–6.7)	3.0–7.0
2 h glucose (mmol/l)	46	6.8 (4.9–14.2)	<7.8
Fasting insulin (pmol/l)	43	32 (15–76)	5–69
HOMA-IR[a]	43	1.02 (0.38–2.98)	<2.77

[a] Homeostasis model assessment index

measurements of PEF were observed during the randomized follow-period [30]. However, at 2 years of follow-up PEF increased by 33 l/min (17–50 l/min; $P < 0.001$) [31].

Adverse events

No serious or unexpected adverse events were recorded and none of the patients died.

In total seven patients left the study, six of them during the randomized period—three in each arm of the study.

In the placebo treated group, two withdrew because they felt depressed and had increased weight, one patient left for unknown reasons. The three patients in the GH treatment arm were withdrawn by the investigators, one due to progression of already known diabetes and two due to lack of compliance. One patient left the study during the follow-up period shortly before completion of the study without any reason recorded.

Three patients with impaired glucose tolerance at baseline developed diabetes.

One patient complained of isolated incidents of headache together with nausea within the first two months of treatment, while another patient complained of more or less constant headache throughout the study period.

Two patients developed mild pretibial edema while four patients had regression of pre-existing edema during the 2-year treatment period.

One patient was diagnosed with carpal tunnel syndrome of unknown duration; and underwent surgery for this during the GH study period.

Discussion

Both reduced basal IGF-I levels and low peak GH response to provocative test have been reported in previous studies, with different stimulation tests and corresponding cut-off limits for diagnosing GHD [27, 32, 38–49]. The increased amount of adipose tissue in PWS patients has been proposed to be the explanation of the impaired response to stimulation tests. However, Grugni et al. [40] demonstrated that PWS patients showed a poorer response to the GHRH-arginine stimulation test than a control group of obese patients—also using BMI related cut-off values [40].

Six patients out of 41 fulfilled the very stringent definitions for severe GHD normally accepted for adults [19]. Abnormal function of the GH/IGF-I axis has previously been described in adult PWS patients, suggesting abnormally low values for free IGF-I—even when obesity was taken into account [32]. It is, therefore, plausible that PWS is associated with subnormal GH secretion and IGF-I activity—in accordance with the reduced growth velocity in PWS children, and the increase in skeletal growth in response to GH treatment [2].

Prevalence of diabetes mellitus has previously been estimated to be 25% in adults with PWS [2, 33], despite having less insulin resistance, and lower fasting insulin levels than expected when compared to weight matched controls [34, 35]. In adults with GHD insulin sensitivity is reduced, presumably due to accumulation of visceral fat [19]. A possible explanation for the normal average insulin sensitivity in PWS is the body composition with low amount of visceral abdominal fat tissue [36]. It is well known, that one of the main physiological effects of GH is a decrease in insulin sensitivity. In our study GH treatment did not result in any change in average glucose metabolism [30, 31], in accordance with previous studies [18, 37–39, 41, 42]. On the individual level only three patients had developed diabetes at 2 years of GH treatment, all of whom had impaired glucose tolerance at baseline.

The observed changes in OGTT in the PWS patients during GH treatment are not surprising, but make vigorous surveillance of carbohydrate metabolism in these patients mandatory. Furthermore, in order to avoid overdosing with GH it is advisable to keep IGF-I levels within the normal range for age and gender, although, we in this follow-up study were unable to document any association between absolute or incremental IGF-I values and worsening of glucose tolerance.

Patients with dyslipidaemia have increased risk of cardiovascular disease, and patients with untreated GHD have increased risk of dyslipidaemia [19]. Approximately 30 percent of our cohort had increased LDL-cholesterol at baseline; which is probably not very different from the background population. A small but significant reduction in LDL-cholesterol was seen during the initial GH treatment [30]. However, this effect disappeared during follow-up [31].

Several studies have shown that total body composition in patients with PWS is abnormal with increased amount of fat primarily located subcutaneously [2, 18, 36–39] and reduced LBM [43]. Regional analysis of body composition in PWS has so far only been performed in small cohorts either by CT [37, 42] or (in women only) by magnetic resonance imaging [36].

In the Scandinavian study we demonstrated and confirmed that the amount of VF was low compared to SF in both genders, and that the abdominal fat to a higher degree was located subcutaneously when compared to a healthy group of subjects with similar age and BMI [29]. Adults with PWS are usually severely obese [2, 18, 36, 40, 41, 44–48], in contrast to the present cohort, in which more than 1/3 had a normal BMI. We believe this to be a consequence of the earlier attention to strict dietary measures and organized psycho-social care implemented in recent years.

The Scandinavian Adult PWS Study is the first large scale and long-term double blind placebo-controlled trial with GH treatment in these patients. We observed beneficial effects on both regional (CT) and total body composition (DXA) [30]. When extending GH treatment in an open design up to a total of 2 years, these effects were maintained [31]. Similar changes in body composition after GH treatment have previously been described in a smaller placebo-controlled study [18], as well as in two open labeled studies [41, 42, 47]. One paper has published 5 years observational data in six PWS adults treated with GH, reporting maintenance of the positive effects on body composition [38, 39].

It is an issue to develop a method to identify PWS patients with reduced physical performance. One study of gait has found reduced walking speed in adults with PWS as compared to obese and healthy controls [49]. However, most studies evaluating physical activity in PWS have been performed in children [16, 50, 51]. We applied a test battery as proposed by Guralnik et al. [28, 52] which originally was designed to be a predicator of disability in persons over the age of 70. Our adults with PWS were considerably younger, and we modified the test to include a 10 m walk since the patients managed the 2.4 m walk test easily [53]. The majority obtained a maximum or near maximum score and the test battery was not able to detect any improvements in physical function during GH treatment. This was in contrast to reports from parents and caretakers of improved physical performance during the entire follow-up period. In retrospect, the test battery was not strenuous enough to be able to register improvements in physical performance, and to detect improvements the test might benefit from further modifications, for example by increasing the lengths and duration of the tests. On the other hand, the test battery seems to be better applicable for the registration of impairments. So far, only Gondoni et al. [41] have showed improvement of physical function in adults with PWS in an open labeled study, indicating that a positive effect of GH treatment may be measurable with an appropriate test.

As an indirect assessment of muscle function, we measured PEF, which improved by 12 percent at 2 years of GH treatment. Restrictive ventilatory impairment has been demonstrated in PWS children and adults, mainly due to respiratory muscle weakness [54], and studies with GH in children have demonstrated improved pulmonary function [2, 16, 55]. The improvement on PEF was not seen after 12 months treatment (where only half of the patients had received GH) [30]. It can be argued, that the improvement seen after 2 years of treatment reflects improved technique rather than a real increase in PEF. However, the patients needed full reinstruction on how to perform the test at each visit. Furthermore, the improved muscle function as indicated by the improvement in PEF concurs with the increase in LBM during GH treatment.

Conclusions

Severe GHD as defined by the present strict criteria for adults was infrequent in the present cohort of adults with PWS. However, evidence of reduced activity of the GH/IGF-I axis in PWS was seen and IGF-I increased during GH treatment. As compared to controls body fat was increased and primarily located subcutaneously, while visceral adipose tissue was normal. Accordingly insulin sensitivity and circulating lipids were normal. GH treatment resulted in beneficial changes in body composition with reduced FM and increased LBM. Respiratory muscle function seemed to improve after 2 years of GH treatment. Adverse effects to GH treatment were few. It is, however, important to monitor glucose metabolism since the GH induced insulin resistance might lead to diabetes mellitus in predisposed individuals.

Acknowledgments The Scandinavian study on GH treatment in adults with PWS was supported by grants from Novo Nordisk Scandinavia AB, Malmö, Sweden and Novo Nordisk, Bagsværd, Denmark, The A.P. Møller Foundation for the Advancement of Medical Science, Research Initiative of Aarhus University Hospital, Aarhus University Hospital Skejby Research Foundation, Aase and Ejnar Danielsen Foundation, The Danish Prader-Willi Syndrome Association, The Augustinus Foundation.

Conflict of interest Jens Sandahl Christiansen and Charlotte Höybye are members of the advisory board on the International Outcome study of NordiNet, NordiNet investigators and have received lecture fees from NovoNordisk.

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