Growth Hormone Treatment of Adults with Prader Willi Syndrome and Growth Hormone Deficiency Improves Lean Body Mass, Fractional Body Fat, and Serum Triiodothyronine Without Glucose Impairment: Results From The US Multi-Center Trial

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DISCLOSURE STATEMENT:
HRM is a consultant to MERCK and receives grant support from Lilly and GSK; PDKL is currently employed by Serono. BW and SM received grant support from Pfizer (2003-2005); Lilly, Serono and Pfizer make rhGH, but these products are not approved for PWS; WZ, MF, MC, BP and ALS have nothing to report.
Structured Abstract

Context: Growth hormone (GH) replacement in PWS children has well defined benefits and risks and is used extensively worldwide. Its use in PWS adults has been limited by documentation of benefits and risks, as determined by larger multi-site studies.

Objectives: evaluate effectiveness and safety of GH in GH-deficient genotype positive PWS adults

Design: 12-month open label multicenter trial with 6-month dose-optimization and 6-month stable treatment periods

Setting: Outpatient treatment facilities at 4 US academic medical centers

Patients: Lean and obese PWS adults with diverse cognitive skills, behavioral traits, and living arrangements recruited from clinical populations

Intervention: Human recombinant GH (Genotropin®) initiated at 0.2mg/day with monthly 0.2mg increments to maximum 1.0mg/day, as tolerated

Main Outcomes Measures: LBM and %fat measured by DXA.

Results: LBM increased from 42.65[se2.25]) to 45.47[2.31]kg (P ≤.0001) and %fat decreased from 42.84[1.12] to 39.95[1.34] % (P = .025) at a median final dose of 0.6mg/day in 30 study subjects who completed 6-12 months of GH. Mean fasting glucose, 85.3[3.4]mg/dl, HbA1C 5.5[.2]%, fasting insulin 5.3[.6]µU/ml, AUC-insulin 60.4[7.5]µU/ml, HOMA-IR 1.1[.2] were normal at baseline in 38 study initiators, including 5 diabetics, and remained in normal range. Total T3 increased 26.7%: 127.0[7.8] to 150.5[7.8]ng/dl (P=.021) with normalization in all subjects, including 6(20%) with baseline T3's≥ 2 SD's below mean. Mildly progressive ankle edema was the most serious treatment emergent adverse event (5 patients).

Conclusions: This multi-center study demonstrates that GH improves body composition, normalizes T3, and is well tolerated without glucose impairment in PWS genotype adults.
Prader Willi Syndrome (PWS) is a complex genetic disorder involving failure of expression of paternal alleles in the PWS region of chromosome 15q11-13. The PWS phenotype is variable, but is usually characterized by hyperphagia, childhood growth failure with adult short stature, hypogonadotropic hypogonadism, and body composition abnormalities including markedly increased body fat and decreased lean mass and diminished bone mineral density. Several studies have documented the presence of growth hormone (GH) and insulin-like growth factor-1 (IGF-I) deficiency.

Growth hormone replacement in children with PWS is approved worldwide and is well accepted, and extensively used due to well documented benefits and defined safety profile. (1-10). Prior studies suggest that GH therapy may be beneficial in adults with PWS (11)(12). However, previous data are limited by small sample sizes and inclusion of subjects lacking genetic confirmation. GH use in PWS adults remains controversial due to pleiotropic effects of GH on glucose homeostasis and perceived potential risks for diabetes, The Metabolic Syndrome (MS), and other obesity- and age-related co-morbidities in overweight and obese PWS adults. Prior studies have not specifically addressed adults with wide ranges of intellectual performance, behavioral abnormalities, growth hormone exposure, metabolic characteristics, gonadal status, and living situations.

We conducted a one-year, multi-center open label study to evaluate safety and effectiveness of GH therapy in genotype positive, growth hormone deficient (GHD) PWS adults. This open label study of somatropin (Genotropin®) was designed to replicate clinical practice and provide guidelines for GH use in diverse PWS subjects of varying age, growth hormone exposure, sex-steroid replacement, cognitive function, living situations, and co-morbidities at 4 clinical sites.

The primary study endpoint was change in DXA-determined lean body mass (LBM) and percent body fat. Secondary measures included glucose tolerance and insulin response curves, and Metabolic Syndrome components. Thyroid function tests, including T3, were also measured to characterize the thyroid axis in PWS adults and GH-mediated thyroid effects on lean mass, as reported in non-PWS GHD adults (13-15).

**Subjects and Methods**

**Study Population**

Adults with a molecular diagnosis of PWS were recruited from clinical populations at 4 US sites. Study inclusion criteria were age greater than 18, naive to growth hormone or off therapy for a minimum of 12 months, basal sex and age-specific IGF-I SDS ≤1 SD, stable estrogen/progesterone or testosterone replacement (in subjects receiving gonadal replacement), and evidence of dietary control of weight prior to study enrollment. Patients were excluded from the study if they had a major systemic illness, severe mental retardation, active tumors, poorly controlled diabetes, or evidence of diabetic retinopathy. The study was approved by Institutional Review Boards at each of the four study sites and informed consent was obtained from both study subjects and their guardians.

**Growth hormone stimulation tests**

GH was measured at baseline and 0, 30, 60, 90, and 120 minutes following the administration of 500 mg L-dopa, prepared in oral unit-dose formulation from pharmaceutical grade L-dopa powder (Bryce Laboratories, Stamford, CT). Secretogogue selection was based on the presumed hypothalamic level of the GH secretory defect in PWS and the desirability of avoiding intravenous infusion in the study subjects. All subjects were tested in the AM in the fasted state. GHD was defined a priori as a peak response ≤ 10 µg/L.

**Study protocol**

The study was conducted between 2002 and 2005. Patients were seen monthly for the first 3 months and at 6 months for a dose optimization phase and at subsequent 3-month intervals to evaluate treatment response, record anthropometric and behavioral data, monitor side-effects and obtain serial IGF-I determinations. GH dosing was initiated at 0.2mg/day and increased monthly in 0.2mg.
increments, as tolerated, unless the IGF-I was ≥1 SD, in which case the GH dose was decreased to the prior level for the remainder of the study. The primary study endpoints were DXA-determined LBM and %fat. Sample size calculations were based on the power to detect a 5% change at a significance of .05.

Outcome and safety measures

Body composition was determined at baseline and study completion by DXA (Hologic QDR instruments, Bedford, MA). IGF-I’s were obtained at the GH stimulation test, treatment initiation and 1-month intervals for the first 3 months and 6- and 12-month follow-up visits and were sent to a single standard reference laboratory.

Adverse events were assessed at each study visit. Baseline and follow-up electrocardiograms and cardiac ultrasounds were performed in all subjects. Baseline sleep studies were not included in the initial protocol, but were added to determine study eligibility in patients with clinical symptoms suggestive of obstructive sleep apnea.

Anthropometric measures and behavioral assessments

Height, weight, waist, and hip circumference, and blood pressures were measured in by a single trained observer per site. Waist circumference was recorded at the narrowest diameter between the xiphoid process and the iliac crest; hip circumference was defined as the widest diameter below the umbilicus. Dietary review and a 20-item behavioral assessment form were completed at all study visits by the accompanying parent or caregiver.

Growth hormone, glucose tolerance testing, thyroid function tests, and other laboratory determinations

GH levels were measured by a solid phase competitive chemiluminescent enzyme immunoassay (Immune-1000 analyzer, DPC, Los Angeles, CA) with sensitivity of 0.01µg/liter and intra- and interassay coefficients (CVs) respectively 2.9 and 4.2%.

All laboratory examinations were performed in a single central laboratory (with the exception of glucose and lipid profiles, sent to affiliated clinical laboratories).

Standard 75-gram oral glucose tolerance tests were performed in the morning following a 12 hour fast in 33 non-diabetic patients. Insulin levels were determined with a DPC-Immune assay with intra- and inter-CV’s 5.7% and 5.9%, and no cross reactivity to pro-insulin.

Serum TSH, total and free T4, and total T3 were measured in the fasting state at baseline, 6 months, and study completion using a DPC-chemiluminescent assay (respective CV’s 10.0 and 6.2%, 6.7 and 6.7%, 5.5 and 5.0% and 10.1 and 7.5%). Serial IGF-I measurements were assessed at every study visit (Esoterix Endocrine Laboratories, Calabas Hills, CA), CV’s 8.3% and 5.4%.

Total fasting adiponectin was collected during the baseline oral glucose tolerance tests in 32 non-diabetic subjects and assayed with an ELISA kit from LINCO (Bellerica, MA), CV’s 6.2 and 9.3%.

Components of the Metabolic Syndrome and relevant covariates were assessed at baseline in 38 GHD patients (Table 1) using NCEP guidelines (16). HOMA-IR was calculated by the formula: fasting insulin (microunits/milliliter) times fasting glucose (millimoles/liter) divided by 22.5 (17).

Statistical Analyses

Statistical analyses were conducted using SPSS v.13.0. Non-normally distributed variables were log-transformed or evaluated with non-parametric procedures. Data were expressed as the mean ± SE and the median.

Data analysis included: One-way Analysis of Variance (ANOVA) to compare group means for continuous variables across sites; paired t-tests to determine mean group change from baseline at indicated time-points; parametric and non-parametric correlations; and linear and logistic regression for covariate adjustment of main treatment effects. All reported P-values are exact and represent 2 tailed significance tests. Last observation carried forward (LOCF) were utilized to record final observations in patients who did not complete
the 12-month final visit. No other corrections were made for missing data.

**Results**

*Baseline characteristics of the initial study population*

Thirty-eight (25 women and 13 men, mean age 30.5±1.5 years and BMI 34.7±1.7 kg/m²) met GHD inclusion criterion and were included in the study. Mean and median GH peak responses in the study qualifiers were respectively 2.06±.32 and 1.35 µg/L (Figure 2). Thirty-four subjects had GH peaks ≤4µg/L; 19 had flat response curves with peak ≤1 µg/L. Baseline mean±se and median IGF-I and IGF-I standard deviation scores in the 38 study initiators were respectively 119.1±11.1 and 102.0µg/ml and -1.9±0.1. Baseline characteristics of this study population are summarized in Table 1. Prior GH use was reported in 8(21.1%) of subjects; 13(34.4%) were on standard dose sex steroid replacement or had regular menses at the onset of the study.

Metabolic parameters of the initial 38 study participants, including 5 with diabetes include: fasting glucose 85.3±3.4 mg/dl and hemoglobin A-1C 5.5±.2%, fasting insulin and AUC-insulin 5.3±.6 µU/ml and 60.4±7.5 µU/ml and HOMA-R of 1.1±.2. Glucose tolerance tests performed on 33 non-diabetic patients identified one patient with both fasting hyperglycemia and impaired glucose tolerance (IGT). Including the 5 patients with diabetes, only 6 of 33(18.1%) with complete data met NCEP consensus criteria for Metabolic Syndrome. Abnormal sex-specific waist circumferences (men: >102 cm and women: >88 cm), present in 24(63.2%) of 38 subjects, was the most common MS component. Sixteen (of 35 with complete data) or 45.7% had abnormal sex-specific HDL levels and 8(25%) (of 32 with available data), had abnormal baseline triglycerides, while only 4 of 38 (10.5%) met MS blood pressure criteria.

Mean adiponectin was 20.8±2.8 mg/L, 23.4±3.5 mg/L in women and 15.0±4.1 mg/L in men (P=.163 for ANOVA by sex). Significant direct and inverse correlates of adiponectin included age (rho= 0.621, P=.000), BMI (rho= -.553, P=.002), and fasting insulin (rho= -.511, P=.005).

*IGF-I SDS improved from -1.8±.2 to -0.2±.2 at a median final dose of 0.6mg/day, range: 0.4-1.0mg/day (Table 2). Significant improvements were observed in both LBM and %fat. LBM increased from 42.66±2.25 to 45.47±2.31 kg (P≤.0001) and %fat decreased from 39.95±1.34 % (P=.025). Regression models indicated that these changes were independent of age, initial BMI, sex steroid use, and social setting and were noted in a subset of patients who were evaluated at 6 months. The percent increase in LBM was significantly greater in the male than the female subjects, 6.66 vs. 4.35%, whereas the decrease in %fat mass, -4.35 vs. -6.28% was not (Figure 3). (This is reported as a post hoc analysis, since the study was not powered to permit stratification by sex for the main treatment effect.)

HbA1C did not vary significantly during the study: 5.4±.2 % to 5.5±.2 %. Fasting glucose increased from 81.1±2.6 mg/dl to 87.6±3.0 mg/dl (6.6%), but remained in normal range in 27 patients (including 3 with diabetes) with available data (P=.01). Fasting 4.9±.7 µU/ml and AUC-insulin, 53.4±6.2 µU/ml increased to 7.7±1.2 µU/ml and 80.3±10.5 µU/ml (P's .006, .003) in 22 tested (non-diabetic) study participants. HOMA-IR increased from 1.1±.1 to 1.9±.3 (P=.007). Management of diabetes did not change during the study. Of 29 patients with available data, the prevalence of MS increased after GH to 31.0% (9 patients).

*Thyroid measurements*

None of the subjects were known to be hypothyroid or were on thyroid hormone replacement at enrollment. However, among the 30 study completers, 6 subjects (20%) had total T3's ≥2 SD's below the assay mean (127.0 ng/dl) at baseline. Baseline thyroxine (T4), free T4 (FT4) and thyroid stimulating hormone (TSH) were within the normal range for all subjects. Statistically significant GH-induced changes in totalT3 and totalT4 were observed (Figure 4).
Total T3 increased by 26.7 % (P=.021), 127.0[7.8] to 150.5[7.8] ng/dl, with normalization in all subjects. Total T4 decreased by 7.8 % (P=.051), 8.6[.4] ng/dl to 7.9[.4] ng/dl. TSH, 1.56[.25] µU/dl vs. 1.49[.17] µU/dl and FT4, 1.1[.1] vs. 1.0[.0] ng/dl were essentially unchanged. Correlation of T3 and LBM changes just failed to reach significance (P=.06).

Behavioral assessment scores

Symptom scores completed by family or health aides present at the study visits demonstrated a reduction in total symptom score from a mean 8.3±4.7 to 6.13±4.5, (P=.04) in 15 subjects with evaluable symptom checklist scores.

Adverse Events

Mild progression of preexisting ankle edema (5 patients) was the most serious treatment emergent adverse event; one patient withdrew from the study because of myalgias associated with lower leg swelling. There was no other evidence of fluid retention for these or any other subjects at baseline or during the study. Baseline cardiac ultrasounds revealed previously unidentified, clinically insignificant valvular defects in two of 38 study subjects, but were otherwise essentially normal and were unchanged in follow up studies.

Discussion

Growth hormone treatment effects

Growth hormone mediated improvements in growth, body composition, and respiratory function have been documented in studies of children with PWS (1-6). Accordingly, GH was approved for “long-term treatment of pediatric patients with growth failure due to Prader-Willi Syndrome (PWS)” in the United States in 1999 and is currently the only medication specifically approved for use in PWS. Although most adults with PWS have deficiencies of GH or the GH/IGF axis and suffer similar body composition abnormalities as compared to both children with PWS and adults with GH deficiency(18), data on GH treatment of adults with PWS is limited. In a study of 13 adults with genetic confirmation of PWS, a 12 month course of GH increased LBM (3.7±0.9 kg) and decreased %fat (-3.8±1.3%), (12) with persistence of these effects in 6 subjects who elected to continue treatment for a median of 5.1 years (19).

Our results from a multicenter study provide additional information regarding GH status and treatment effectiveness in a larger population of adults with a confirmed diagnosis of PWS. For our investigations, L-dopa was selected as the GH secretagogue based on the presumption that a GH secretory defect in PWS would likely be at the hypothalamic level. This testing confirmed GHD in 38/40 (95%) of subjects, in association with low IGF-I levels.

During the initial 6 months of the protocol, the GH doses were progressively increased as described in the Methods. During this period, 5 patients experienced ankle-limited swelling and one subject had associated myalgias leading to discontinuation of GH treatment, while others remained in the study with adjustment of GH dose. The mean GH dose, 0.6 mg/day (~0.008 mg/kg/day for our study population) at dose optimization is similar to doses used in non-PWS adult GHD(20) and is substantially lower than the 0.03-0.05 mg/kg/day used in pediatric PWS and GHD.

Over the subsequent 6 months of the study, the GH doses were maintained at a constant level. Our results provide confirmation that GH treatment, even over a relatively short period of time, leads to significant improvements in body composition in adults with PWS, including a decrease in %fat and increased LBM and, typically, are independent of changes in BMI, a measurement that is not sensitive to shifts in body compartments. These improvements in LBM may be important in PWS, a condition in which LBM is severely deficient.

Monitoring of glucose homeostasis was an important objective of the multicenter study, although baseline data indicated low prevalence of glucose abnormalities and insulin resistance, as reported in some (23-25), but not all prior studies (26). Despite modest increases in glucose and insulin, HbA1c and all measures of insulin and glucose homeostasis remained within normal limits in all study subjects, including 5
with diabetes and one with IGT. Thus, although GH may worsen IGT or diabetes, this was not demonstrated in this limited study population.

The prevalence of Metabolic Syndrome, unexpectedly low at baseline (6 patients (18.1%)), increased after GH (among 29 patients with available data) to 31.0% (9 patients). In 3 patients this increase was secondary to increased triglycerides and corresponded to weight gain, directly attributable to documented dietary lapses, presumably unrelated to GH treatment.

The thyroid axis in Prader Willi Syndrome

The thyroid axis is generally considered to be normal in PWS subjects as prior studies have not revealed any abnormalities in standard determinations of TSH, total or free T4 or total and free T3 (23, 27-29). However, Bray and colleagues reported TRH stimulated TSH values in 9 PWS subjects that were two standard deviations above those of 6 obese controls despite normal basal TSH, T3 and T4 levels in their cohort of 40 very obese subjects (mean BMI = 47.0 kg/m²), suggesting mild impairment in the hypothalamic-pituitary control system for the thyroid, (23) and Tauber reported hypothyroidism demarcated by low T4 and/or elevated TSH levels in 32% of 28 children with PWS, 23 of whom were genotype positive (29). In a recent study of 47 children and adults with PWS, Butler reported an incidence of hypothyroidism comparable to the general population based on TSH and T4 levels. However, despite a normal reported mean total T3 level, 137±((SD)37)ng/dl, the level appeared low (<80 ng/dl) on inspection of individual bar graphs in 5 of 41 (12%) of subjects with available data (28).

To our knowledge, the observed baseline T3 abnormalities in 20% of growth hormone deficient PWS subjects and their normalization with GH therapy are unique. However, they are consistent with reports in children with PWS (30) and in non-PWS GHD adults, documenting dose dependent enhancement of extrathyroidal T4 to T3 conversion(13-15)(31) and suppression of circadian thyrotropin levels following the administration of GH (15, 32), as well as with other widely reported subtle, but notable complexities in the interaction of GH with the hypothalamic-pituitary-thyroid axis (32). The concomitant group mean reduction in total T4 levels following GH (8.6 to 7.9 ng/dl, P=.05) provides additional evidence of increased deiodination of T4 in our PWS subjects and supports the hypothesis that peripheral conversion of thyroxine to triiodothyronine may contribute to growth hormone mediated enhancement of resting energy expenditure and lean body mass (15).

Type 2 iodothyronine deiodinase, predominantly found in skeletal muscle has been identified as the major source of plasma T3 in euthyroid subjects(33). Theoretically, activity of this deiodinase may be low in PWS, a condition characterized by a remarkably low level of LBM, and the resultant low T3 levels may contribute to pathology in some patients. Augmentation of this deiodinase activity by increasing LBM, e.g. with GH therapy, could be particularly important in patients with PWS. Although our data correlating changes in LBM and T3 did not reach statistical significance (P=0.06), the observed trend and response to GH treatment are consistent with this hypothesis. In summary, our findings suggest, that, as in other GHD subjects, PWS adults may have subtle thyroid abnormalities, especially T3 alterations, which are reversed with GH replacement and that this may contribute to amelioration of the uniquely abnormal body composition associated with Prader Willi Syndrome.

Other qualitative findings

Profound baseline differences in cognitive and social skills, living situations, behavioral symptoms, and GH exposure limited acquisition and interpretability of GH-mediated changes in quality of life (e.g., the study cohort included two subjects who attended college, 8 young adults who received GH throughout childhood, several of whom attended regular educational programs, and institutionalized, morbidly obese older adults with significant co-morbidities). Behavioral assessment scores based on rating scales of typical PWS-associated symptoms demonstrated improvement in number and degree of many behavioral abnormalities, consistent with other studies (34).
Formal assessment of physical fitness was not included in our Multi-center trial due to the wide variation in baseline exercise capacity precluding the use of a single study instrument. However, in qualitative data elicited from open-ended questions, study subjects previously engaged in regular exercise reported increased aerobic conditioning (increased duration on treadmill, biking or lap swimming) and physical strength (load bearing in weight training) in supervised activities. Both study subjects and their guardians also reported increased energy levels, improved attention spans, and general sense of well-being. Future studies should include pre and post treatment measurements of these important domains in suitable patient subsets.

**Strengths and limitations of the study**

Our study design did not include a placebo arm as the study investigators could not justify the use of injections without discernible benefit to our study population. At the study initiation, 2002, GH mediated body composition changes had been well documented in multiple studies of GHD adults and GH had been approved for growth failure in children with PWS, although its safety profile had not been established in adults with PWS. The preservation of normal fasting blood sugar and HbA-1C, even among 5 diabetics enrolled in the study, supports the relative safety of GH in this population, but, clearly, additional follow-up studies will be necessary to determine long term consequences of GH treatment in this population.

We believe the diverse nature of the study population – the wide range of ages, co-morbidities and cognitive and social skills of our subjects – contributed to reliability and validity of the study findings.

Although, the low prevalence of PWS in the general population precluded restriction of the study cohort to a homogeneous sample, control for the influence of potentially important covariates, including sex steroid status, were addressed with multivariate analyses. The absence of effect modification of the GH-mediated improvements in body composition despite extreme ranges in various baseline characteristics, including age (17-49 years), weight (42.3-145.5 kilograms), and BMI (22.0-63.6 kg/m²), as well as sex steroid status and growth hormone exposure, suggests that the study findings may be extrapolated to additional heterogeneous adult PWS cohorts. The notable exception, effect modification of LBM by sex, with greater treatment response in men than women, has been previously reported in GH replacement studies of GHD adults with(12) and without PWS (20).

In conclusion, our 12 month multi-center trial in 38 diverse GHD genotype positive PWS adults demonstrates that GH therapy improves LBM and %fat, and normalizes IGF-I levels without glucose impairment. The incidence of Metabolic Syndrome was low at baseline and, with the exception of triglyceride elevations, attributable to dietary lapses in 3 study subjects, did not change appreciably during GH treatment. In addition our findings suggest that total T3 levels may be low in a significant proportion of this population and are normalized with GH therapy. As with treatment of non-PWS adult GHD subjects, some individuals may have significant GH-mediated water retention during dosage optimization, mandating judicious GH initiation, dosage adjustment and careful monitoring. Long-term studies will be necessary to further delineate the risks and benefits of GH in this population.

**Acknowledgments**

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LEGENDS FOR TABLES AND FIGURES

Table 1. Metabolic characteristics of 38 growth hormone deficient PWS adults at study enrollment

Table 2. Metabolic and hormonal results in 30 PWS adults at baseline and after GH treatment

Figure 1. Flow Chart of the study
Figure 2. Growth hormone stimulation tests with L-dopa in 38 PWS adults who qualified for the study
Figure 3. Changes in Lean Body Mass and Percent Fat in male and female study subjects following growth hormone Treatment
Figure 4. Thyroid function tests at baseline and following growth hormone treatment
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<td>110</td>
<td>131 (70-201)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>122.6 (±10.5)</td>
<td>107.0</td>
<td>239 (49-288)</td>
</tr>
<tr>
<td>Adiponectin (mg/dl)</td>
<td>20.8 (±2.8)</td>
<td>16.0</td>
<td>0.0 (0.0-50.0)</td>
</tr>
<tr>
<td>Lean Body Mass (kg)</td>
<td>42.6 (±2.1)</td>
<td>38.7</td>
<td>48.2 (22.0-70.2)</td>
</tr>
<tr>
<td>Percent Fat</td>
<td>43.0 (±1.1)</td>
<td>44.4</td>
<td>21.3 (31.5-52.8)</td>
</tr>
<tr>
<td>IGF-I (µg/ml)</td>
<td>119.1 (±11.1)</td>
<td>102.0</td>
<td>313.0 (37.0-350.0)</td>
</tr>
<tr>
<td>Base IGF SDS</td>
<td>-1.9 (±0.1)</td>
<td>-2.0</td>
<td>3.07 (-3.22- -0.15)</td>
</tr>
</tbody>
</table>

**Table 1.** Metabolic characteristics of 38 growth hormone deficient PWS adults at study enrollment
Table 2. Metabolic and hormonal results in 30 PWS adults at baseline and after GH treatment

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline Mean (±se)</th>
<th>Baseline Median</th>
<th>After GH treatment Mean (±se)</th>
<th>After GH treatment Median</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>151.7 (±2.2)</td>
<td>150.6</td>
<td>147.6 (±5.6)</td>
<td>150.0</td>
<td>0.431</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>78.7 (±4.7)</td>
<td>71.8</td>
<td>78.8 (±5.1)</td>
<td>71.6</td>
<td>0.707</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>33.7 (±1.8)</td>
<td>32.4</td>
<td>32.6 (±1.6)</td>
<td>31.2</td>
<td>0.194</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>101.4 (±4.1)</td>
<td>98.3</td>
<td>98.4 (±3.3)</td>
<td>96.5</td>
<td>0.299</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>116.0 (±2.7)</td>
<td>116.0</td>
<td>116.4 (±2.1)</td>
<td>113.5</td>
<td>0.866</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>72.4 (±2.1)</td>
<td>70.0</td>
<td>70.6 (±1.8)</td>
<td>71.0</td>
<td>0.364</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>81.1 (±2.6)</td>
<td>82.0</td>
<td>87.6 (±3.1)</td>
<td>86.0</td>
<td>0.010</td>
</tr>
<tr>
<td>2-hour glucose (mg/dl)</td>
<td>90.0 (±5.8)</td>
<td>90.5</td>
<td>129.9 (±11.6)</td>
<td>123.5</td>
<td>0.015</td>
</tr>
<tr>
<td>AUC-insulin (µU/ml)</td>
<td>53.4 (±6.2)</td>
<td>50.6</td>
<td>80.3 (±10.5)</td>
<td>73.0</td>
<td>0.006</td>
</tr>
<tr>
<td>Fasting Insulin (µU/ml)</td>
<td>4.9 (±0.7)</td>
<td>4.7</td>
<td>7.7 (±1.2)</td>
<td>5.7</td>
<td>0.003</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.1 (±0.2)</td>
<td>0.9</td>
<td>1.9 (±0.3)</td>
<td>1.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Hemoglobin A-1C (%)</td>
<td>5.4 (±0.2)</td>
<td>5.0</td>
<td>5.5 (±0.2)</td>
<td>5.3</td>
<td>0.174</td>
</tr>
<tr>
<td>Total T3 (ng/dl)</td>
<td>127.0 (±7.8)</td>
<td>128.0</td>
<td>150.5 (±7.8)</td>
<td>142.0</td>
<td>0.021</td>
</tr>
<tr>
<td>Total T4 (µg/dl)</td>
<td>8.6 (±0.4)</td>
<td>8.5</td>
<td>7.9 (±0.3)</td>
<td>7.8</td>
<td>0.053</td>
</tr>
<tr>
<td>Free T4 (ng/dl)</td>
<td>1.1 (±0.05)</td>
<td>1.1</td>
<td>1.1 (±0.03)</td>
<td>1.0</td>
<td>0.104</td>
</tr>
<tr>
<td>TSH (µU/ml)</td>
<td>1.6 (±0.3)</td>
<td>1.3</td>
<td>1.6 (±0.2)</td>
<td>1.4</td>
<td>0.985</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>194.1 (±7.8)</td>
<td>190.0</td>
<td>189.1 (±7.3)</td>
<td>180.0</td>
<td>0.423</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>51.0 (±3.2)</td>
<td>49.5</td>
<td>51.1 (±2.9)</td>
<td>49.5</td>
<td>0.949</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>119.4 (±7.2)</td>
<td>113.0</td>
<td>117.4 (±6.6)</td>
<td>111.5</td>
<td>0.779</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>118.1 (±11.0)</td>
<td>97.0</td>
<td>179.3 (±48.4)</td>
<td>98.0</td>
<td>0.200</td>
</tr>
<tr>
<td>Lean Body Mass (kg)</td>
<td>42.7 (±2.3)</td>
<td>38.6</td>
<td>45.5 (±2.3)</td>
<td>42.3</td>
<td>0.000</td>
</tr>
<tr>
<td>Percent Fat</td>
<td>42.8 (±1.1)</td>
<td>43.7</td>
<td>40.0 (±1.3)</td>
<td>40.3</td>
<td>0.025</td>
</tr>
<tr>
<td>IGF-I (µg/ml)</td>
<td>121.8 (±17.3)</td>
<td>107.0</td>
<td>290.8 (±37.2)</td>
<td>299.5</td>
<td>0.001</td>
</tr>
<tr>
<td>IGF SDS</td>
<td>-1.8 (±0.2)</td>
<td>-1.9</td>
<td>-0.2 (±0.2)</td>
<td>-0.4</td>
<td>0.000</td>
</tr>
<tr>
<td>No. of Metabolic Syndrome variables</td>
<td>1.4 (±0.2)</td>
<td>1.0</td>
<td>1.45 (±0.2)</td>
<td>1.0</td>
<td>0.646</td>
</tr>
</tbody>
</table>
Figure 1. Flow Chart of the Study

US Adult Prader-Willi Syndrome Study

- UCLA consented* (n=6)
- WMC consented* (n=8)
- Columbus consented* (n=16)
- St. Louis U consented* (n=10)

40 underwent GH Stimulation Test

2 non-GHD

38 met study entrance criterion for GHD
GH peak ≤ 10 ng/ml (34 pts ≤ 5 ng/ml)

8 did not complete trial
2 never started GH
2 lost to follow-up
4 withdrew after 3-6m
(1 due to AE’s)

30 completed 6-12 month GH replacement trial

*Both study subjects and guardians signed consents.
Figure 2. Growth hormone stimulation tests with L-dopa in 38 PWS adults who qualified for the study
Figure 3. Changes in lean body mass and percent fat in male and female study subjects following growth hormone treatment.
Figure 4. Thyroid function tests at baseline and following growth hormone treatment.