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Effect of Growth Hormone Replacement Therapy on Metabolic Characteristic in Young Adults with Prader-Willi syndrome

Aneta Durmaj[1], Sebastian Szewczyk[1], Maria Libura[2], Magdalena Góralska[3*]

[1]Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland
[2]Medical Education and Simulation Centre, Collegium Medicum, University of Warmia and Mazury, Olsztyn, Poland.
[3]Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Warsaw, Poland

Abstract

Introduction: Prader-Willi syndrome (PWS) is a complex, multisystemic genetic disorder caused by the lack of expression of paternally inherited genes in the PWS critical region on chromosome 15. Growth hormone (GH) deficiency is a common endocrine problem in PWS patients not only in childhood but also in adults. Recombinant human growth hormone (rhGH) therapy serves not only to achieve an ultimate height within a desired range, but also to compensate for metabolic abnormalities, lower body mass and reduce fat mass percentage (%FM). The aim of the study was to assess the metabolic profile of adults with PWS and compare a GH treated cohort (childhood onset of treatment) with an untreated cohort.

Material and Methods: This is a retrospective, non-randomised study including 25 young adults diagnosed with PWS. Patients were divided into 2 groups depending on GH replacement therapy (1st group never treated and 2nd treated since childhood within the framework of the Therapeutic Health Programme in Poland). The treatment was monitored with respect to IGF-1 serum levels. In all patients BMI, FM%, carbohydrate metabolism and thyroid function were assessed and statistically analyzed to compare outcomes both groups.

Results: The group of GH treated patients, which comprised 19 individuals, had a statistically lower FM%, BMI, as well as a normal IGF-1 level in contrast to the untreated cohort. Insulin level was within normal ranges across all groups, yet lower levels were attested in the GH-treated individuals. HOMA-IR index was statistically lower in the GH-treated group. No significant differences between analysed groups were observed in regard to thyroid function.

Conclusions: While metabolic disturbances are common in a young-adult with PWS, GH replacement therapy is safe and effective in achieving not only proper growth in children, but also normal metabolic profile in adults. It plays a crucial role in reducing the individual metabolic risk and should be an important part of PWS treatment programs.

Keywords: Prader-Willi syndrome (PWS), GH therapy, Body composition, Metabolic profile.

Introduction

Prader-Willi syndrome (PWS) is a complex, multisystemic genetic disorder caused by imprinting abnormalities on chromosome 15. It results from the lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 region [1]. PWS occurs with an estimated prevalence of 1/10,000-1/30,000 in populations [2]. PWS may manifest with variable clinical presentations.

A complex hypothalamic-pituitary dysregulation is currently thought to be partly responsible for PWS phenotype: it is a recognized cause of compulsive appetite, and endocrine problems, like growth hormone (GH)/insulin-like growth factor I (IGF-I) axis dysfunction, diminished functional activity of the gonads, premature adrenarche, secondary adrenal insufficiency, impaired glucose tolerance, hypothyroidism [3-5]. Nowadays, the clinical presentation of PWS is changing due to diagnosis in early infancy and treatment.

***Correspondence:** Goralska M, Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Warsaw, Poland.

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Altered glucose metabolism is frequently observed in PWS. Diabetes mellitus type 2 (T2DM) has been reported in 25% of adult PWS population. This metabolic issue is characterized by hyperglycemia caused by insulin resistance [4] The greater risk of T2DM seems to be particularly pronounced after puberty and in obese subjects, with a mean age of onset at about 20 years [6]. Central hypothyroidism, characterized by normal thyroid stimulating hormone (TSH) value and low free thyroxine (FT4) level appears to be a significant feature both in children and adults with PWS [7].

GH deficiency is present in the great majority of children with PWS [8]. Furthermore, it has been demonstrated to persist in many adults with PWS [9], but the benefits of treatment in adulthood have been less evidenced than in the paediatric population, particularly among those over 40 years of age [10]. Unfortunately, due to GH deficiency in adulthood, worsening of body composition and metabolic profile has been observed [11-13].

Recombinant human growth hormone (rhGH) therapy in PWS is administered in childhood as well as in adults. It serves two primary targets. The first is to achieve a ultimate height within the normal range for a given population, while the second is to compensate for metabolic abnormalities and improve the body mass and fat percentage disrupted by absolute or qualified GH deficiency [14].

In Poland rhGH therapy is available for adult PWS patients within the framework of the national Therapeutic Health Programme (THP) since 2016. To achieve the metabolic and physiological effects of GH, adults need significantly lower doses than the paediatric population, with dose reduction at 30-50%. Monitoring of the therapy is based on clinical presentation and IGF- 1 level, aimed at keeping it in the upper part of the reference range. Maintaining the body weight within the normal range is a requirement for continuation of GH treatment in Poland [15]. Undeniably, individuals with Prader-Willi syndrome need multispecialty medical care.

The aim of the study is to compare the metabolic profile of young adults with PWS with respect to the GH treatment status.

Material and Methods

Patients and Treatment Schedule

This study was a retrospective, non-randomised trial. Twenty five-patients, (12 females and 13 males), all with confirmed PWS, with mean age 20, 5 years (± 18-27 years), were included in the study. Characteristics of the group are given in **Table 1**. Patients were admitted to the Department of Internal Medicine and Endocrinology between 2018 and 2019. GH therapy was administered to 19 patients, with a median GH dose during the observation term of 0.45 mg/d in a daily subcutaneous injection (range 0.3-1.6 mg/d) according to the guidelines. Serum (IGF-1) levels are used to evaluate GH deficiency and to monitor GH replacement therapy within THP. Physical examination included measuring height, weight and body fat percentage in fasting conditions. Standing height was determined by a stadiometer WPL150. Body weight (to nearest 0.1kg), and body fat percentage were measured with Tanita Body Composition Analyser Type TBF- 300 MA. Body Mass Index (BMI) was defined as weight (kg) / height (m^2). Following the World Health Organization criteria, the BMI cut off points of 18.5-25.0 to define normal weight, 25.0-30.0 to define overweight and >30.0 to define obesity, were used. Fasting blood glucose tests was used to assess for diabetes. Complete thyroid function tests was performed to confirm the diagnosis of hypothyroidism.

Insulin was measured in the blood samples. HOMA-IR (homeostatic model assessment of insulin resistance), a measure of insulin resistance, was calculated according to the standard formula [17-20] ((fasting insulin (mU/mL) × fasting glucose (mg/dL))/405), and insulin resistance when the result was over 0, 3, were confirmed.

Table 1: Characteristic of patient's general parameters.

Variables	Total (25)	GH-treated patients(19)	Untreated patients (6)
Age	20.5 years (18-27)	20.15 (18-27)	21.5 years (18-26)
Height (m)	1.66 ± 0.09	1.674 ± 0.10	1.621 ± 0.03
Weight (kg)	74.65 ± 22.15	70.06 ± 19.07	89.18 ± 26.69
Sex	Females - 12	Females - 11	Females - 2
	Males - 13	Males - 8	Males - 4
BMI [18.5 24.9](kg/m²]	24.40 [18.03-46.47]	24.06 [18.03-36.57]	36.90 [21.00-46.48]
FM%	26.1 ± 11.87	22.61 ± 9.92	34.48 ± 12.99

Note: Data expressed as mean with standard deviation, for age the range were given.
Abbreviations: m- meters, kg- kilograms

Table 2: Characteristic of patient's depending on BMI.

Male Untreated (4)	Mean BMI	36,33914058	**Female Untreated (2)**	Mean BMI	28,75
	Standard deviation BMI	8,328508335		Standard deviation BMI	7,75
Male Treated (8)	Mean BMI	26,41696786	**Female Treated (11)**	Mean BMI	23,51872145
	Standard deviation BMI	4,837685897		Standard deviation BMI	4,969243194
All Male	Mean BMI	29,72435877	**All Female**	Mean BMI	24,32353354
	Standard deviation BMI	7,784674439		Standard deviation BMI	5,804933679

Statistical Analysis

Results are expressed as means with standard deviation (SD) for parametric data and median with ranges for nonparametric data. Distribution of the continuous variables was calculated with the Shapiro-Wilk test [16]. Comparisons between continuous data were performed using paired t-test [17] (for parameters with normal distribution) or Mann-Whitney U test [18] (for parameters with distribution deviations). Tests were considered significant for p-values < 0.05. Analyses were performed using software STATISTICA 13.3.721.1 64-bit (PL).

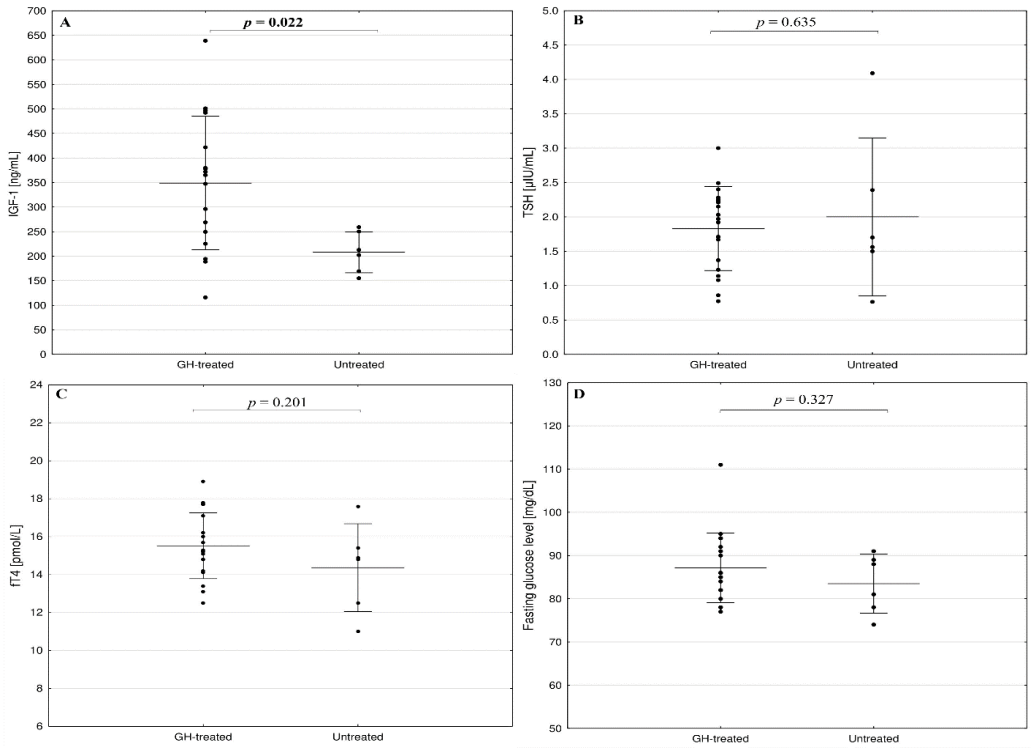
Results

The measurements of the study subjects are given in **Figure 1**. While 12 PWS subjects were within the overweight range, 13 had normal weight. We compared the variables taking into account the GH-treatment status. According to the statistics, GH-treated patients had a statistically significant lower FM% and BMI degree and higher IGF-1 level in comparison to untreated individuals. One patient presented impaired fasting glycaemia (IFG) during the treatment, yet no statistically significant difference between analysed groups was observed. Insulin levels and rate were within the normal range across all groups. Insulin resistance, expressed as HOMA-IR rate, was normal in all patients; however, its level was lower in the GH-treated individuals. At the time of the study, ten patients (6 males, 4 women) had T2DM and were treated with metformin (500-2000 mg per day). Thirteen individuals suffered from hypothyroidism (6 males) and were biochemically maintained on L-thyroxine substitution. One patient had an abnormal TSH level, all patients were euthyroid. There were no differences between analysed cohorts **Table 3**. All our patients need sex steroid replacement therapy.

Table 3: Results depending on GH-treatment.

Variables	**Total** (25)	**GH-treated Patients**(19)	**Untreated Patients** (6)
IGF-1 [117-436] (ng/mL)	312.20 ± 133.57	348.94 ± 135.96	208.08 ± 41.85
TSH [0,53-3,59] (µlU/mL)	1.87 ± 0.75	1.83 ± 0.61	2.00 ± 1.15
fT4 [12-20,6] (pmol/L)	15.24 ± 1.90	15.52 ± 1.73	14.37 ± 2.32
Fasting glucose [70-99] (mg/dL)	86.28 ± 7.81	87.16 ± 8.06	83.5 ± 6.83
Insulin [2,6-24,9] (µlU/mL)	8.34 [2.90-23.40]	6.04 [2.90-23.40]	8.72 [4.42-19.70]
HOMA-IR	0.073 [0.001-0.254]	0.069 [0.001-0.254]	0.104 [0.054-0.224]

Note: Data expressed as mean ±SD and median with ranges. The reference values are given.



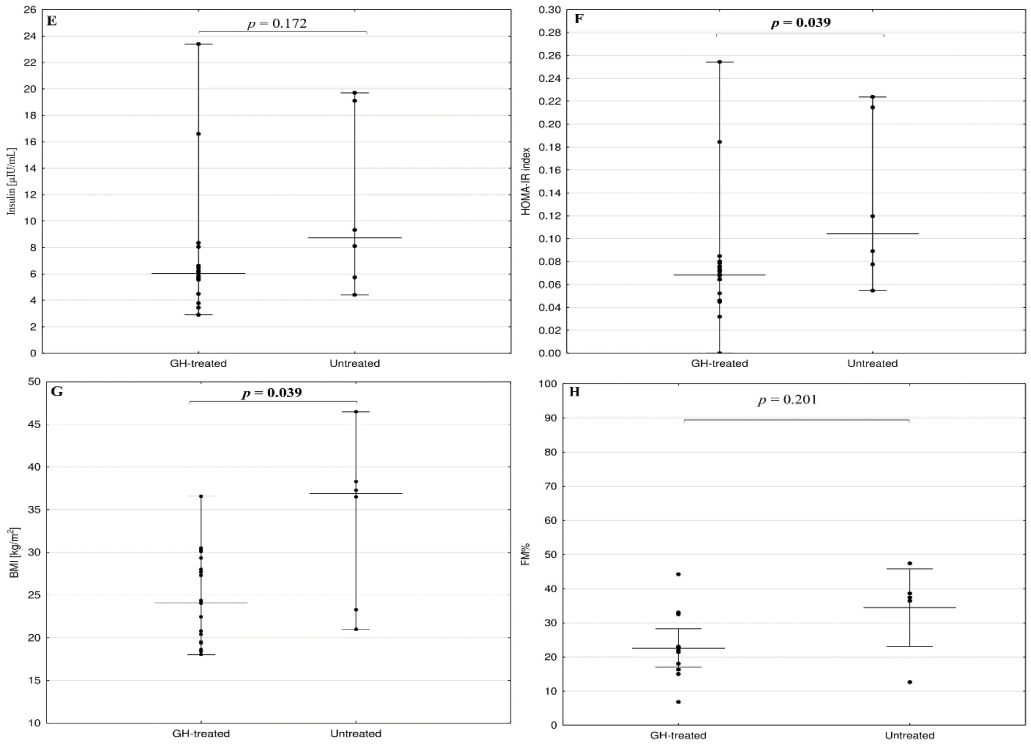


Figure 1: Comparison of variables between GH-treatment and untreated groups. (A) shows IGF-1 level, (B) and (C) shows TSH and fT4 levels, (D) is a fasting glucose level, (E) and (F) shows insulin level and insulin resistance level, respectively, (G) is a BMI level, (H) shows fat mass percentage.

Discussion

The literature about GH therapy in a lifelong care of PWS patients is limited, even though the benefits of such treatment in children are well established [19]. It has been demonstrated to affect not only the final bodily height but also metabolism and body composition. Anabolic effects of GH include an increase in lean body mass, motor strength as well as a decrease in fat mass in comparison to untreated children [1]. Non-growth-stimulating effects of GH should be taken into consideration while continuing GH therapy in adulthood [20].

Inconsistent information about the prevalence of GHD in adults with PWS can be found in the literature. It ranges from 8 to 55% [20], depending on the study groups, provocative tests used as well as the cut-offs point established to define deficiency. In a Dutch cross-sectional study of 60 young adults with PWS none of the patients fulfilled the consensus criteria for adult GHD [21]. Conversely, a United States study confirmed GHD in 38 of 40 subjects (95%) [22].

Adult PWS patients are clinically affected by GH insufficiency, but the exact mechanisms are not fully understood. Clinical evidence is emerging showing the beneficial effects of GH therapy regardless of whether the criteria of GHD are met, even when GH provocative testing is normal [19, 20]. Overall, the duration of GH-therapy proves significant in maintaining good body composition and preventing complications of obesity in adults with PWS, which was also confirmed in our study . Studies have shown a deterioration of body composition and higher BMI after cessation of GH therapy in PWS patients. Placebo-controlled trial showed a dramatic increase of fat mass in a placebo cohort [23]. GH-treatment leads to significant increase in lean body mass and decrease in percent fat independently of age, initial BMI, sex steroid use and social settings. Improvement of IGF-1 level is noticeable [22].

While comparing groups in our study we also observed the positive impact on body composition, with lower BMI and total percent body fat in GH-treated cohort. Data about the influence of GHT on metabolic disorders in the patients with PWS are scarce. There are some doubts whether only GHT is responsible for impairment of glucose homeostasis in subjects prone to develop type 2 diabetes (T2DM). T2DM has been reported in 25% of adults with PWS with a mean age of onset of 20 years. Large meta-analysis of 134 adults and investigator-initiated trial of 46 patients shows small increase in fasting glucose and trends towards higher insulin and insulin resistance [24, 25]. Insulin resistance, expressed as HOMA-IR, showed a tendency to increase with age with a peak in adolescents in PWS. Reasons for the decreased insulin sensitivity in PWS include visceral obesity, lower GH levels, and higher ghrelin levels for obesity [4]. In Scandinavian study on forty-six adults with PWS, 12 months of GH therapy improved body composition. BMI and total fat mass were reduced, whereas. During the one year treatment, no major side effects were seen, and glucose metabolism was not affected [9]. Results of the United States Multicentre Trial also did not demonstrate glucose impairment during GH treatment. HbA1c and all measures of insulin and glucose remained within normal limits in all study subjects, including five with diabetes and one with IGT [22]. According to Kuppens et al. placebo-controlled investigation GH treatment resulted in similar glucose and insulin level during OGTT. Only fasting glucose and insulin were slightly

higher, although both remained within normal ranges and caused no pathology. Considering other positive effects of therapy, they concluded, that patients benefit from continuation of GH treatment without safety concerns regarding metabolic health [26].

In our study the similar conclusion was drawn. Although ten subjects from 19 treated by GH had T2DM and were treated with oral hypoglycaemic agents alone, their glucose results were within normal range and did not worsen during the therapy. By significant reduction in fat mass and body mass it could be beneficial, because fat mass and overweight are strictly connected with T2DM. Some studies also support explanation, that deterioration of body composition due to discontinuation of GH can result in worse metabolic health profile and the GH benefits overweight minimal effect on glucose and insulin homeostasis [22].

The complications related to obesity are thought to be the main reasons for reduction in life expectancy in rates in PWS patients [2]. According to retrospective studies yearly mortality rates in PWS patients older than 30 years were estimated around 7% [27]. The improvement in weight control remains the most important goal of any PWS treatment program.

The abnormalities of thyroid function are discussed in literature and published data are discordant. Majority of studies were investigated on the paediatric population [28, 29] and suggested the lack of thyroid function disturbances. Butler et al. reported an incidence of hypothyroidism similar to general population rate [5], while there are also studies reporting prevalence at 20-30% [30]. However, novel data from Italian study confirm the relevant presence of hypothalamic-pituitary-thyroid axis dysfunction in PWS [7]. Some researchers suggest that although not meeting the criteria for hypothyroidism, there may be a mild impairment in the hypothalamic-pituitary axis in PWS patients. Mogul el al. found that 6 of 30 patient's hat total T3 values of at least 2 SD below the assay mean. They observed statistically significant GH-induced changes in total T3 and total T4. Total T3 increased with normalization in all patients, total T4 decreased, TSH and free T4 were essentially unchanged. Reduction in total T4 level after GH treatment supports hypothesis that peripheral conversion of T4 o T3 may contribute to GH-mediated enhancement. Activity of deiodinase may be low in PWS because of low level of lean body mass. It leads to low T3 level and contribute to pathology. GH therapy could be beneficial for PWS patients by increasing of lean body mass and thus augmentation of deiodinase activity [22]. It is recommended to measure TSH and FT3, FT4 after diagnosis of PWS and control then approximately every 6 months during GH therapy [15].

In our study 10 of 19 patients treated with GH and 3 of 6 patients without GH therapy were on L-thyroxin replacement therapy. All of them were euthyroid at the enrollment. We did not reach any statistically significant differences, but in GH-treated cohort TSH and FT4 were slightly higher than in GH-untreated one, what was opposite to expectance. Long-term studies on larger population are required to analyze thyroid status of our patients.

As patients with PWS require a lifelong therapy transition from pediatric to adult health care is considered a very important and not easy because of many physical and behavioral problems. Usually, PWS patients are still unable to live independently and they stay under parental protection. Parental involvement is a great help for maintenance of the same approach to food, environment, and treatment [31].

GH therapy is beneficial also after reaching desired height in adults. The metabolic and physiological demand for GH is significantly lower in adulthood; ca. 30–50% of the dose used in the pediatric population. The initial dose for adults of 0.1-0.2 mg/day is recommended, and a subsequent titration of the doses should be based on clinical response and IGF-1 levels within the upper range of the reference range. In Poland transition from pediatric to adult health care is quite smooth. Patients can continue GHT if they fulfill the inclusion criteria based on metabolic homeostasis. Due to quite strict requirement patients and their family put much effort in maintenance nutritional restriction and desired BMI. In our study none of the patients have been excluded from the program that indicates that they were under good metabolic control. It may have contributed to the lack of adverse effect of GH therapy in our study [15].

Conclusions

This study is a report on the prevalence of metabolic disturbances in a young-adult population of PWS. Overall, PWS subjects show a no prevalence of altered glucose metabolism or thyroid dysfunction connected with decreasing fat mass percentage and BMI. Our data confirm the crucial role of growth hormone treatment in the reduction of the individual metabolic risk clustering in PWS, and thus reinforce the concept that such treatment in adults with PWS is safe and profitable and remains the most important goal of any PWS management program.

The limitation of our study is that it was carried out on a small group of patients, but they will still be monitored and we will have a follow-up.

Further longitudinal studies, however, are needed to better understand the endocrine and metabolic factors in PWS individuals.

Conflict of Interest

The authors declare that they have no conflict of interest.

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