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Effects of one-year low-dose growth hormone (GH) therapy on body composition, lipid profile and carbohydrate metabolism in young adults with childhood-onset severe GH deficiency confirmed after completion of growth promotion

Wpływ rocznej terapii małą dawką hormonu wzrostu na skład ciała, profil lipidów i metabolizm węglowodanów u młodych dorosłych ze stwierdzonym w dzieciństwie ciężkim niedoborem hormonu wzrostu potwierdzonym po zakończeniu leczenia promującego wzrastanie

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Abstract

Introduction: The symptoms of GH deficiency (GHD) in adults include: abnormalities in body composition, unfavourable lipid profile, early atherosclerosis and impaired quality of life. The aim of the study was the selection of patients with confirmed severe GHD from among all the children treated due to GHD, who could benefit from GH therapy continuation in adulthood and the optimization of GH dosage in young adults with severe GHD.

Material and methods: The study group consisted of 54 young adults (38 male), age 17.6 ± 1.5 years, with childhood-onset GHD, who had reached final height.

At least 1 month after the GH therapy withdrawal, the second evaluation of GH secretion was performed in all the patients. In 24% of patients, permanent severe GHD (PSGHD) was confirmed, but a group of 9 patients (4 male) was involved in renewed GH therapy.

Results: The renewed GH therapy gave positive effects, including a significant increase in fat-free mass and a decrease in fat mass, and a significant decrease in LDL-cholesterol, but connected with an insignificant decrease of HDL-cholesterol serum concentration and improved results of quality of life (QoL) assessment. During the therapy, an insignificant increase of fasting insulin was observed, with no change in fasting glucose and only a slight increase in HbA_1c percentage. A decrease of insulin sensitivity was also observed, but both insulin secretion and the values of insulin resistance indices still remained within the reference range.

Conclusions: The observed positive effects on body composition, lipid metabolism and QoL, together with the absence of adverse events, confirm the indications for GH therapy in young adults with severe GHD. **(Pol J Endocrinol 2008; 59 (4): 292–300)**

Key words: *severe GHD, GH therapy, body composition, lipid profile, carbohydrate metabolism, insulin resistance, quality of life*

Streszczenie

Wstęp: Niedobór hormonu wzrostu (GHD) u dorosłych charakteryzuje się między innymi: nieprawidłowym składem ciała, zaburzeniami profilu lipidowego, wczesną miażdżycą oraz pogorszeniem jakości życia. Celem badania było wyodrębnienie pacjentów z ciężkim przetrwałym GHD, spośród grupy pacjentów z rozpoznanym w dzieciństwie, leczonym GHD, oraz ocena korzystnego wpływu kontynuacji terapii GH w życiu dorosłym, a także ustalenie optymalnej dawki GH u młodych dorosłych osób z ciężkim GHD.

Materiał i metody: Badaniem objęto 54 osoby (38 mężczyzn), w wieku 17,6 ± 1,5 roku z rozpoznanym w dzieciństwie GHD, które uzyskały wzrost ostateczny. U wszystkich pacjentów po okresie — co najmniej — 1 miesiąca od zaprzestania leczenia promującego wzrastanie, przeprowadzono kolejną ocenę wydzielania GH. Ciężką przetrwałą postać GHD stwierdzono u 13 (24%) pacjentów, ale do ponownego leczenia GH włączono tylko 9 osób (4 mężczyzn).

Wyniki: Obserwowano korzystny wpływ ponownego włączenia terapii GH na skład ciała (znamienny wzrost beztłuszczowej masy ciała i zmniejszenie tłuszczowej masy ciała), profil lipidowy (znamienne obniżenie stężenia cholesterolu frakcji LDL, jednakże z towarzyszącym nieznamiennym obniżeniem stężenia cholesterolu frakcji HDL) oraz poprawę wyników testów oceniających jakość życia (QoL). Podczas terapii obserwowano nieznamienny wzrost stężenia insuliny na czczo, bez zmian dotyczących stężenia glukozy na czczo oraz z jedynie nieznacznym wzrostem odsetka HbA_{1c}. Obserwowano również zmniejszenie insulinowrażliwości, chociaż stężenie insuliny na czczo i wskaźniki insulinooporności pozostawały w zakresie wartości referencyjnych.

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Wniosek: Korzystne zmiany dotyczące składu ciała i profilu lipidów oraz QoL przy braku powikłań wskazują na potrzebę leczenia hormonem wzrostu młodych osób dorosłych z ciężkim GHD. **(Endokrynol Pol 2008; 59 (4): 292–300)**

Słowa kluczowe: *ciężki niedobór GH, terapia GH, skład ciała, profil lipidów, metabolizm węglowodanów, insulinooporność, jakość życia*

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Introduction

In recent years, severe GHD has been defined as a separate disease, requiring an accurate diagnosis and substitutive GH therapy administration [1–3]. The symptoms of GHD in adults include: abnormal body composition, reduced bone mineralization, increase of fat body mass, unfavourable lipid profile, reduced cardiac performance [1]. Long-lasting severe GHD increases mortality rate due to cardiological complications and incidence of bone fractures, and deteriorates quality of life [4].

Most of the patients treated with GH in childhood do not require continuation of this therapy as adults. According to current data, a diagnosis of severe GHD is confirmed in adulthood only in the minority of patients with childhood-onset GHD [5–7]. The diagnostic criteria for GHD in adults include clinical signs and symptoms of the disease and decreased GH secretion in provocative tests in patients with previously compensated cortisol, thyroxin and sex steroid deficiencies, if present [8]. Due to the appropriate selection of patients requiring continuation of GH therapy in adult life, repeated evaluation of GH secretion after completion of growth-promoting therapy should be performed. In accordance with current recommendations [8–11], the test of choice in adults is the insulin tolerance test (ITT). In patients with contra-indications to this test (coronary heart disease, epilepsy), an alternative test should be performed. The most reliable test seems to be that with arginin and somatoliberin (GHRH) administration [12]. The test with clonidine, routinely performed in children, seems less useful in the diagnosis of GHD in adult patients [9, 13, 14]. In 1997, during a Conference in Port Stephens, it was proposed that only one provocative test be performed to confirm childhood-onset GHD [9]. It seems more appropriate to perform two GH provocative tests in cases of previously diagnosed isolated GHD, but only one test in patients with multiple pituitary hormone deficiency (MPHD), for the confirmation of severe GHD in adulthood [11].

The standardized algorithm of repeated evaluation of the hormonal state of the patient, as well as the recommended time-point for renewed GH therapy administration and the rules of its continuation, have not been established so far. Even so, the problem of GH therapy optimization in adult life remains a subject of interest for many researchers [9, 10].

Low-dose growth hormone therapy in adults is not as expensive as in children. Moreover, preventing the complications of GHD in adult patients is economically favourable.

The aim of the study was the selection of patients with confirmed severe GHD from all the subjects who were treated during childhood with GH for growth promotion due to GHD, who could benefit from GH therapy continuation in adulthood as well as optimizing GH dosage and monitoring GH therapy in young adults with severe GHD.

The Local Ethical Committee approved the study protocol. Informed consent was obtained from all patients involved.

Material and methods

Patient recruitment

Analysis comprised 54 young adults (38 male, 16 female), age 17.6 ± 1.5 years (mean ± SD), with childhood-onset GHD, who completed GH therapy in our department and reached final height (FH) in 2004–2006.

The diagnosis of GHD in childhood was based on the combination of auxological and hormonal criteria, *i.e.* decreased GH peak (below 10 ng/ml) in 2 stimulating tests — with clonidine 0.15 mg/m^2 orally and with either glucagon 30 μg/kg *i.m.* (not exceeding 1 mg) or insulin 0.1 IU/kg *i.v.* In 41 patients, a diagnosis of isolated GHD was established, while the remaining 13 suffered from MPHD. The group with MPHD included 7 children with pituitary stalk interruption syndrome (PSIS), 3 patients who had had neurosurgery due to *craniopharyngioma*, 1 boy with isolated severe pituitary hypoplasia and 2 patients (girls) with severe GHD together with *diabetes insipidus* (DI).

All the patients were treated with GH in a dose of 0.18 ± 0.02 mg/kg/week (0.55 ± 0.07 IU/kg/week) and withdrawn when FH with closed bone epiphyses was attained.

The patients' height SD score at therapy onset (H_0SDS) was –2.38 ± 0.71, being improved up to –1.20 ± 0.75 when FH was achieved. Most of the patients (47 out of 54) reached FH within normal range. Height gain was not observed in 7 patients — all with isolated, partial GHD (GH peak in childhood from 5.6 ng/ml to 7.4 ng/ml) and with normal insulin-like growth factor 1 (IGF-1) secretion before the therapy. At least 1 month

after the GH therapy withdrawal, the second evaluation of GH secretion (retesting) was performed on all the patients. In patients with either MPHD or GHD coexisting with DI, a single stimulating test - ITT with insulin — in a dose 0.1 IU/kg *i.v.* was performed, while in those with previously diagnosed isolated GHD, the same test was followed by a second one (with arginin 0.5 g/kg and GHRH 1 μg *i.v.*). The cut-off values of GHD peak confirming severe GHD in adulthood were as follows: 3 ng/ml for ITT and 9 ng/ml for the test with arginin and GHRH, according to Aimaretti et al. [12]. The diagnosis of partial GHD was established when GH peak was between 3.0 ng/ml and 5.0 ng/ml in ITT or between 9.0 ng/ml and 16.5 ng/ml in the arginin-GHRH test. Higher GH secretion in stimulating tests was recognised as normal, leading to the diagnosis of transient GHD.

For the second part of the study, a group of 9 patients (4 male, 5 female) was included from those with confirmed permanent severe GHD (PSGHD).

Evaluation during low-dose GH therapy

The therapy with low-dose GH was started after at least 12 but no more than 36 months from the cessation of growth-promoting treatment. At the onset of therapy, the mean age of the patients was 20.1 ± 2.1 years. The therapy was continued for 1 year under control of IGF-1 and IGF-binding protein-3 (IGFBP-3) concentrations. A fixed daily GH dose of 0.3 mg (0.9 IU) was applied during the entire therapy period in 8 out of 9 patients, while, in 1 patient, the dose was increased due to low levels of IGF-1 up to 0.4 mg (1.2 IU), thus leading to normalisation of IGF-1 secretion.

Before the renewed GH administration, auxological, biochemical and hormonal evaluation of the patients was performed. The patients' height, weight as well as waist and hip circumferences were measured. Then body mass index (BMI) and waist:hip ratio were calculated. The following parameters of body composition were assessed: fat mass (FAT), free fat mass (FFM), fat tissue percentage (FAT%) and total body water (TBW). Fasting glucose, glycosylated haemoglobin (HbA_{1c}), total cholesterol (TCh), LDL-cholesterol (LDL-Ch) and HDL-cholesterol (HDL-Ch), triglycerides (TG), as well as serum IGF 1 and IGFBP-3 concentrations were measured in the morning hours before the first GH injection. In all the patients, oral glucose tolerance test (OGTT) was performed with 75.0 g glucose administration. Glucose and insulin levels were assessed at 0, 60 and 120 minutes of the test, and insulin resistance indices, HOMA-IR and IRI according to Belfiore (IRI-Belfiore), were calculated [15, 16].

Auxological measurements, glucose metabolism and lipid profile, together with IGF-1 and IGFBP-3 assessment were repeated after 1 year of GH therapy, according to the same protocol as the previous treatment.

Both during the examinations preceding the repeated GH therapy inclusion and during the period of its administration, all the patients received an appropriate substitution of other deficient hormones, *i.e.* L-thyroxin, hydrocortisone, sex steroids and desmopressin, when necessary. The accuracy of the applied doses of the drugs was confirmed by appropriate laboratory analyses.

The patients' quality of life (QoL) was assessed before and after 1 year of low-dose GH therapy using a QoL Assessment of GHD in Adults (QoL-AGHDA) questionnaire, consisting of 25 questions with "yes" or "no" answers [17]. The higher the number of "yes" answers, the more impaired the patient's QoL; scores equal to or over 6 are defined as abnormal.

Laboratory and statistical methods

Growth hormone concentrations were measured by hGH IMMULITE and DPC assay, calibrated to WHO IRP 80/505 standard. Serum IGF 1 and IGFBP-3 concentrations were assessed by IMMULITE, DPC assays, calibrated to WHO NIBSC 1st IRR 87/518 standard for IGF 1 and WHO NIBSC Reagent 93/560 standard for IGFBP-3. For comparison among children of different age and sex, IGF-1 concentrations were expressed as IGF-1 SDS, according to DPC reference data. For calculation of IGF-1/IGFBP-3 molar ratio, the following molecular masses were used: 7.5 kDa for IGF-1 and 42.0 kDa for IGFBP-3 [18]. Biochemical analyses related to the assessment of glucose metabolism and lipid profile were performed with standard kits used in routine diagnostics. Body composition was assessed using the method of bioelectrical impedance — Tanita body fat analyser model TBF 410, based on the principles of leg–to–leg bioelectrical impedance analysis (BIA). A good agreement between BIA and the dual-energy-X-ray absorptiometry (DEXA) method for estimating changes in body composition was described [19].

Statistical analysis included non-parametric tests, as the distribution of most of the analysed parameters (assessed by Kolmogorow-Smirnov test) was not consistent with normal distribution. For comparison between the groups of patients in the same time point, the Mann-Whitney U test for independent samples was applied, while comparisons between the results obtained before and after 1 year of GH administration were performed using the Wilcoxon signed rank test for dependent samples.

Table I. *Patients' height, GH secretion and IGF-1 secretion and bioavailability before GH therapy in childhood and after withdrawal of growth-promoting therapy*

Tabela I. *Wysokość ciała, wydzielanie GH oraz wydzielanie i biodostępność IGF-1 przed włączeniem leczenia GH w dzieciństwie oraz podczas ponownej oceny po zakończeniu terapii promującej wzrastanie*

	Primary diagnosis	MPHD (or GHD & DI)	Isolated GHD
Before GH therapy in childhood	n	13	41
	H_0SDS	–3.39 ± 0.85	–2.25 ± 0.43
	GH peak [ng/ml]	2.10 ± 1.36 (range: 0.6–4.4)	7.0 ± 2.7 (range: 2.3–9.7)
	PSGHDA at rest	**Confirmed**	**Excluded**
1 month after GH therapy withdrawal	FH SDS	–0.65 ± 0.54	–1.36 ± 0.73
	Height SDS gain	2.35 ± 1.16	1.06 ± 0.80
	GH peak [ng/ml] in ITT	0.13 ± 0.08 (range: 0.1–0.4)	16.3 ± 9.7 (range: 6.3–27.8)
	GH peak [ng/ml] in arginin & GHRH test	not performed	34.8 ± 13.2 (range: 10.4–> 40.0)
	IGF-1 [ng/ml]	51.6 ± 21.2 (range: 25.0–93.1)	382.9 ± 152.8 (range: 157.8–856.8)
	IGF-1 SDS	–5.11 ± 1.32	–0.41 ± 1.15
	IGF-1/IGFBP-3 [molar ratio]	0.09 ± 0.02	0.37 ± 0.14

Results

Growth hormone secretory status after completion of growth promoting therapy

Permanent severe GHD according to the criteria for adults (PSGHDA) was confirmed in all the patients with previous diagnosis of either MPHD or GHD and DI. In all but one of them, GH peak in ITT was undetectable (below 0.1 ng/ml) being also extremely low (0.4 ng/ml) in that last case. Conversely, severe GHD was excluded in all the patients with childhood-onset isolated GHD. Moreover, in 37 out of 41 patients in that group, GH peak in ITT exceeded 5.0 ng/ml, thus remaining within the normal range for retesting at the attainment of FH, according to the quoted guidelines [8]. In 30 cases GH peak in ITT even exceeded 10 ng/ml. It should be stressed that there was no overlap of GH peak in ITT between groups and a there was a highly significant difference between them ($p < 0.001$).

Arginine-GHRH test was performed in 41 patients with previous diagnosis of childhood-onset isolated GHD. In 5 patients, GH peak in the test was between 9 and 16.5 ng/ml (12.1 ± 2.6 ng/ml), while in the remaining 36, GH peak exceeded 16.5 ng/ml, even exceeding the upper limit of detection (*i.e.* 40.0 ng/ml) in most cases.

Serum IGF-1 concentration after 1 month from GH therapy withdrawal was decreased in all the patients with childhood-onset MPHD, while in those in childhood-onset isolated GHD presented either normal (in 38 cases) or only slightly decreased (in the remaining 3 ones). The difference between the Groups presented highly significant ($p < 0.005$). Interestingly, the IGF-1/IGFBP-3 molar ratio was also significantly ($p < 0.001$) higher in the first of the analysed groups. More detailed data are presented in Table I.

Efficacy and safety of low-dose GH therapy

IGF-1 and IGFBP-3 secretion

Before the renewed GH therapy, all the patients with PSGHDA had extremely low serum IGF-1 concentrations. After 1 year of low-dose GH replacement, a highly significant ($p = 0.008$) increase of both IGF-1 secretion and its bioavailability (expressed as IGF-1/IGFBP-3 molar ratio) was observed. As mentioned above, IGF-1 levels normalised in all but one patient during administration of the daily GH dose of 0.3 mg (0.9 IU), while, in that last case, a slightly higher GH daily dose, *i.e.* 0.4 mg (1.2 IU) presented an appropriate one. The detailed data are shown in Table II and Figure 1. All the differences between the values obtained at particular analysed time points are marked with * as significant.

Body composition

A positive effect of the renewed GH therapy on the analysed parameters of body composition was observed, including a significant increase of FFM ($p = 0.050$) and decrease of both fat mass ($p = 0.008$) and FAT% ($p = 0.020$). However, a significant increase of TBW

Table II. *Comparison of IGF-1 secretion and bioavailability before and after 1 year of renewed GH treatment*

Tabela II. *Porównanie wydzielania i biodostępności IGF-1 przed i po roku ponownego leczenia GH*

	Before low-dose GH therapy	After 1 year of therapy	p
IGF-1 [ng/ml]	51.3 ± 22.3 (range: 33.4–93.1)	186.9 ± 80.6 (range: 101–390)	0.008*
IGF-1 SDS	–4.88 ± 2.05	–1.57 ± 1.50	0.008*
IGFBP-3 [μg/ml]	3.2 ± 0.9	4.0 ± 0.8	0.028*
IGF-1/IGFBP-3 [molar ratio]	0.09 ± 0.02	0.26 ± 0.09	0.008*

Table III. *Comparison of selected parameters of body composition before and after 1 year of renewed GH treatment*

Tabela III. *Porównanie wybranych parametrów składu ciała przed i po roku ponownego leczenia GH*

		Before renewed GH therapy	After 1 year of GH therapy	p
BMI [kg/m^2]		23.1 ± 3.1	23.7 ± 3.8	0.317
FAT [kg]		19.6 ± 7.2	18.2 ± 6.9	0.008*
FAT%		26.7 ± 8.6	25.6 ± 8.5	0.020*
FFM [kg]		49.8 ± 6.7	52.4 ± 9.5	0.050*
TBW [kg]		36.6 ± 5.1	38.3 ± 7.0	0.028*
FFM-TBW [kg]		13.2 ± 1.7	14.1 ± 2.5	0.069
waist [cm]	males	89.4 ± 11.3	87.9 ± 10.8	
	females	82.1 ±1 0.9	79.7 ± 10.5	
waist: hip	males	0.98 ± 0.17	0.95 ± 0.14	
	females	0.79 ± 0.12	0.76 ± 0.11	

(p = 0.028) should be considered as the main cause of an increase of FFM with normal electrolyte concentrations and with no signs and symptoms of pathological water arrest. The detailed data are presented in Table III and illustrated in Figures 2–3. Significant differences are marked with *. Both waist circumference and waist:hip ratio decreased in all the treated patients; however, due to the small number of cases (only 4 male and 5 female) and sex-related normative data, statistical assessment of those changes was not credible.

Lipid profile

Administration of GH led to a decrease of TCh concentration (but only insignificant) together with a very slight increase if TG level. The positive effect of GH therapy on the lipid profile manifested in a significant (p = 0.038) decrease of LDL-Ch, although connected with an insignificant decrease of HDL-Ch serum concentration. The detailed data are presented in Table IV and in Figure 4.

Glucose homeostasis and insulin sensitivity

Before GH administration, all the patients had normal fasting glucose concentrations and relatively low fasting insulin levels. During the therapy, an insignificant in-

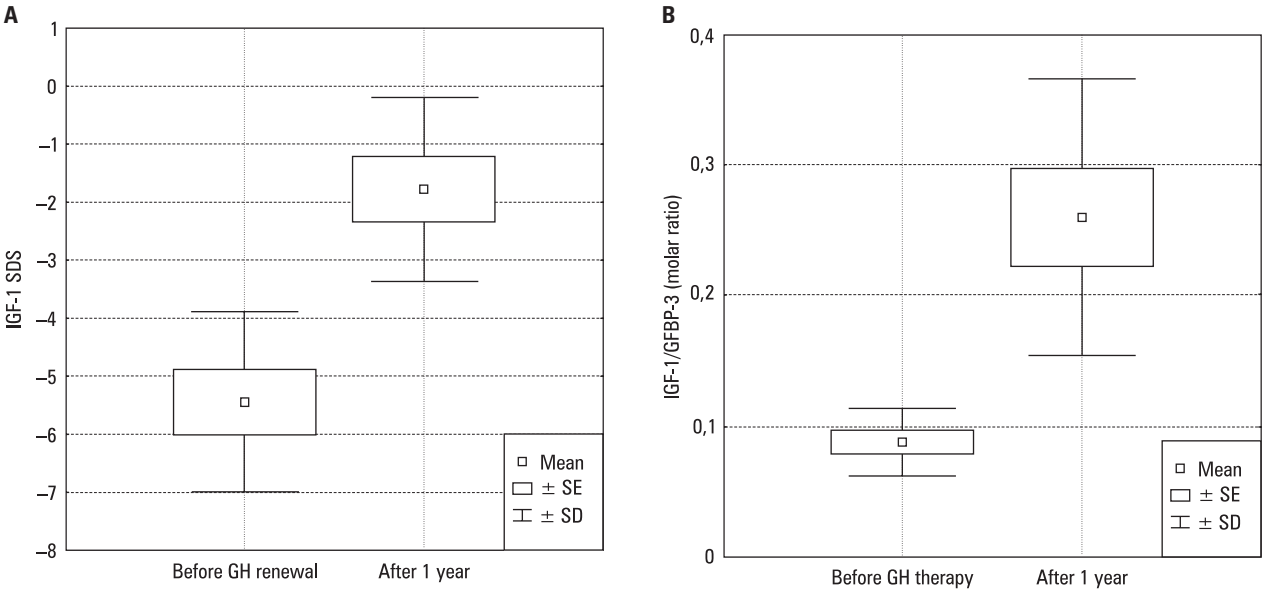

Figure 1A. *Comparison of IGF-1 secretion (expressed as IGF-1 SDS) before and after 1 year of renewed GH treatment.* ***B.*** *Comparison of IGF-1 bioavailability (expressed as IGF-1/IGFBP-3 molar ratio) before and after 1 year of renewed GH treatment*

Rycina 1A. *Porównanie wydzielania IGF-1 (wyrażonego wartością IGF-1 SDS) przed i po roku ponownego leczenia GH.* ***B.*** *Porównanie biodostępności IGF-1 (wyrażonej jako stosunek molowy IGF-1/IGFBP-3) przed i po roku ponownego leczenia GH*

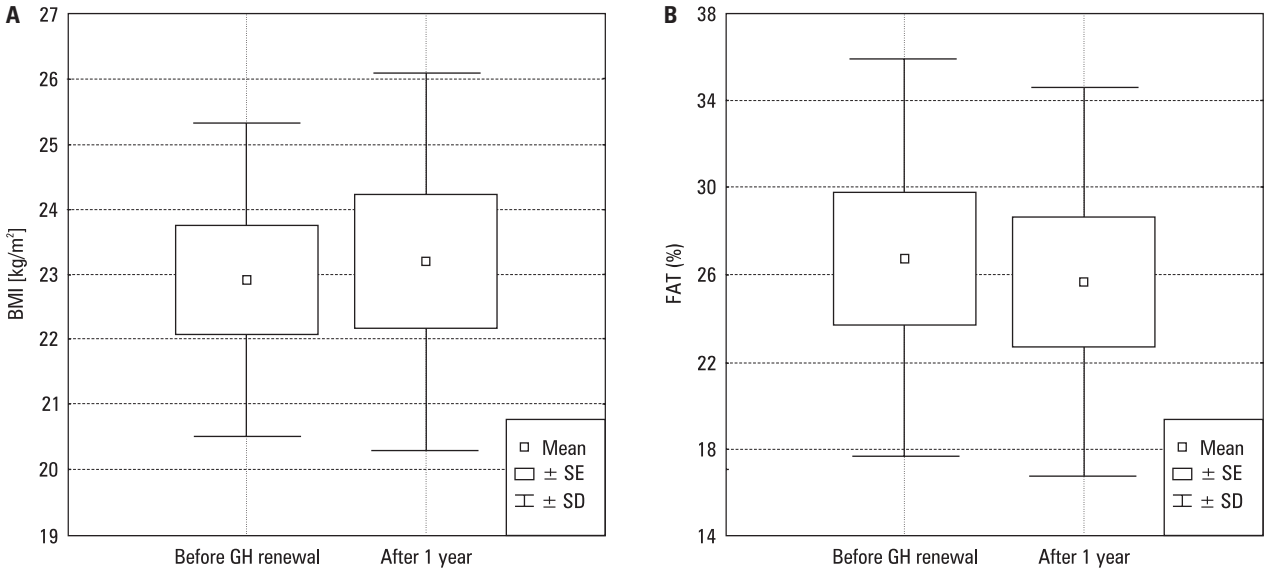

Figure 2A. *Comparison of BMI before and after 1 year of renewed GH treatment.* ***B.*** *Comparison of FAT% before and after 1 year of renewed GH treatment*

Rycina 2A. *Porównanie BMI przed i po roku ponownego leczenia GH.* ***B.*** *Porównanie FAT% przed i po roku ponownego leczenia GH*

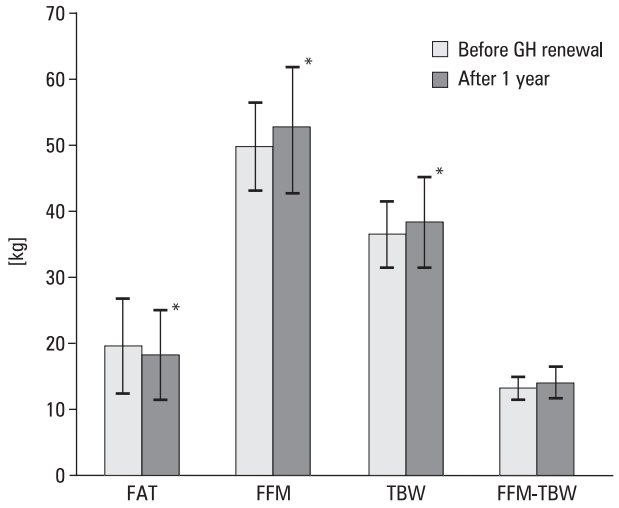

Figure 3. *Comparison of selected parameters of body composition before and after 1 year of renewed GH treatment*

Rycina 3. *Porównanie wybranych parametrów składu ciała przed i po roku ponownego leczenia GH*

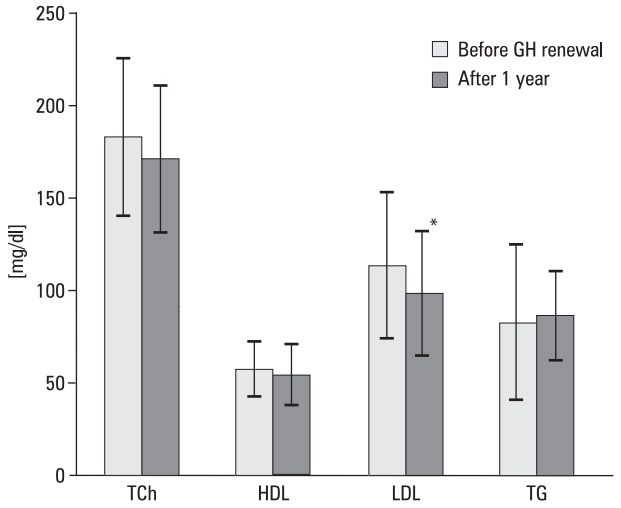

Figure 4. *Comparison of lipid profile before and after 1 year of renewed GH treatment*

Rycina 4. *Porównanie profilu lipidów przed i po roku ponownego leczenia GH*

Table IV. ***Comparison of selected parameters of lipid profile before and after 1 year of renewed GH treatment***

Tabela IV. ***Porównanie wybranych parametrów profilu przed i po roku ponownego leczenia GH***

	Before renewed GH therapy	After 1 year of GH therapy	p
TCh [mg/dl]	184±43	17240	0.155
HDL [mg/dl]	58±15	55±17	0.086
LDL [mg/dl]	114±40	9934	0.038*
TG [mg/dl]	83±43	87±24	0.477

crease of fasting insulin was observed, with no change in fasting glucose and only a slight increase in HbA_{1c} percentage. A decrease of insulin sensitivity was also observed but both insulin secretion and the values of insulin resistance indices still remained within the reference range. Interestingly, an increase of IRI-Belfiore (derived from OGTT) presented significantly, while that of HOMA-IR (calculated from fasting glucose and insulin levels) was insignificant. Moreover, none of the patients discontinued the study or had to reduce GH dose. The detailed data concerning glucose metabolism are presented in Table V and in Figures 5–6.

Table V. *Comparison of fasting glucose, insulin and HbA_{1c} concentrations as well as insulin resistance indices (HOMA-IR and IRI-Belfiore) before and after 1 year of renewed GH treatment*

Tabela V. *Porównanie stężenia glukozy i insuliny na czczo oraz HbA_{1c} i wskaźników insulinooporności (HOMA-IR i IRI-Belfiore) przed i po roku ponownego leczenia GH*

	Before renewed GH therapy	After 1 year of GH therapy	p
Fasting glucose [mg/dl]	71 ± 7	73 ± 9	0.441
Fasting insulin [μU/ml]	2.8 ± 1.4	4.4 ± 2.8	0.173
HbA_{1c} [%]	4.9 ± 0.3	5.1 ± 0.3	0.345
HOMA-IR	4.88 ± 2.65	8.26 ± 6.05	0.116
IRI-Belfiore	0.50 ± 0.26	0.92 ± 0.32	0.036*

Quality of life

After the period of GH therapy withdrawal, *i.e.* just before the onset of low-dose GH treatment, the mean QoL-AGHDA score was 11.2 (range: 6–14) and decreased significantly ($p < 0.05$) to 5.6 (range: 3–8), thus confirming the improvement of QoL during GH administration. The sex-related differences in QoL could not be analysed due to the small number of patients.

Discussion

The positive effects of low-dose GH therapy in adults with severe GHD on body composition, lipid metabolism and QoL are well known. In 2007 Svensson at al. [20] published data on the metabolic and clinical response to one-year GH replacement therapy in 380 adults with GHD. The inclusion criteria in that study (*i.e.* GH peak in ITT below 3 ng/ml) were similar to those applied to the current study. The initial GH dose was lower than that administered in our patients; however, it increased during the therapy up to a dose slightly higher than that used by us. An improvement in all the analysed parameters of body composition, lipid profile and QoL during GH administration was observed, and a negative correlation between the severity of disturbances and the effectiveness of GH therapy was found. The results of a one-year replacement therapy study with a fixed low dose of GH, published by Boguszewski at al. in 2005 were similar [21]. In both studies, no serious side effects were reported. Our results agree with previous observations. It should be stressed, however, that the patients recruited to the current study were younger (mean age: 20.1 years) than in the cited studies — 53.8 years [20] and 40.6 years [21] and the time interval from cessation of growth promoting GH administration was relatively short in our group of patients. It should also be stressed that, despite younger age and short period with no GH therapy, similar abnormalities as found in older patients were observed in the young adults involved in our study. Moreover, the effect of GH therapy administered again in a low dose also presented similarly to those in older age groups of GH-deficient adults.

Both at therapy onset and after one year, our patients had normal BMI, in contrast to the patients reported by Boguszewski at al. [21], who were overweight, probably due to a longer period of untreated severe GHD. However, positive effects of GH administration on lean and fat body mass was observed in both groups.

In our study, lipid profile was normal both before and after one year of GH therapy, but a significant de-

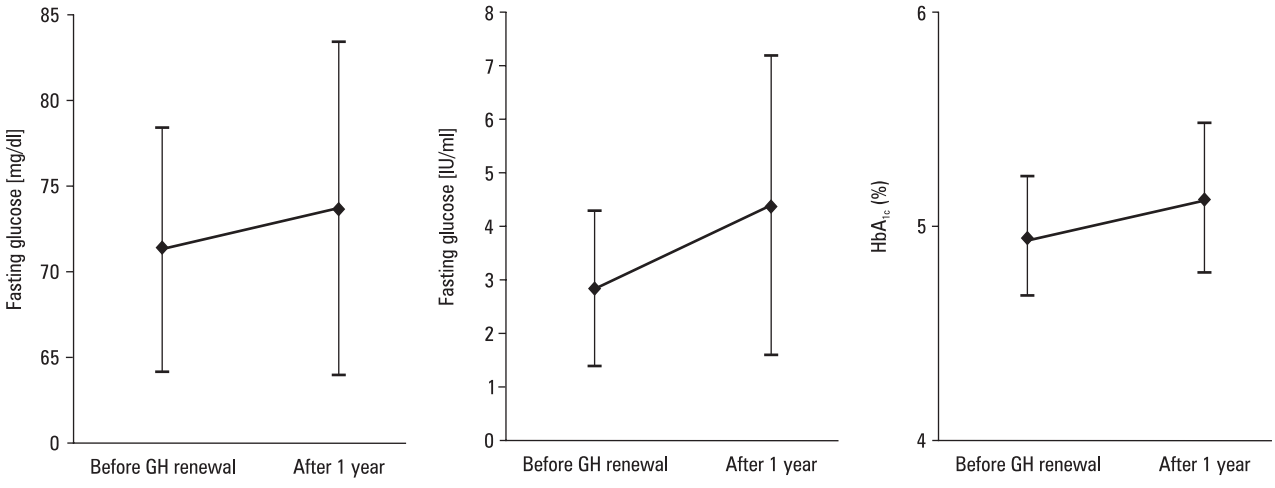

Figure 5. *Comparison of glucose, insulin and HbA_{1c} concentrations before and after 1 year of renewed GH treatment*

Rycina 5. *Porównanie stężenia glukozy, insuliny i HbA_{1c} przed i po roku ponownego leczenia GH*

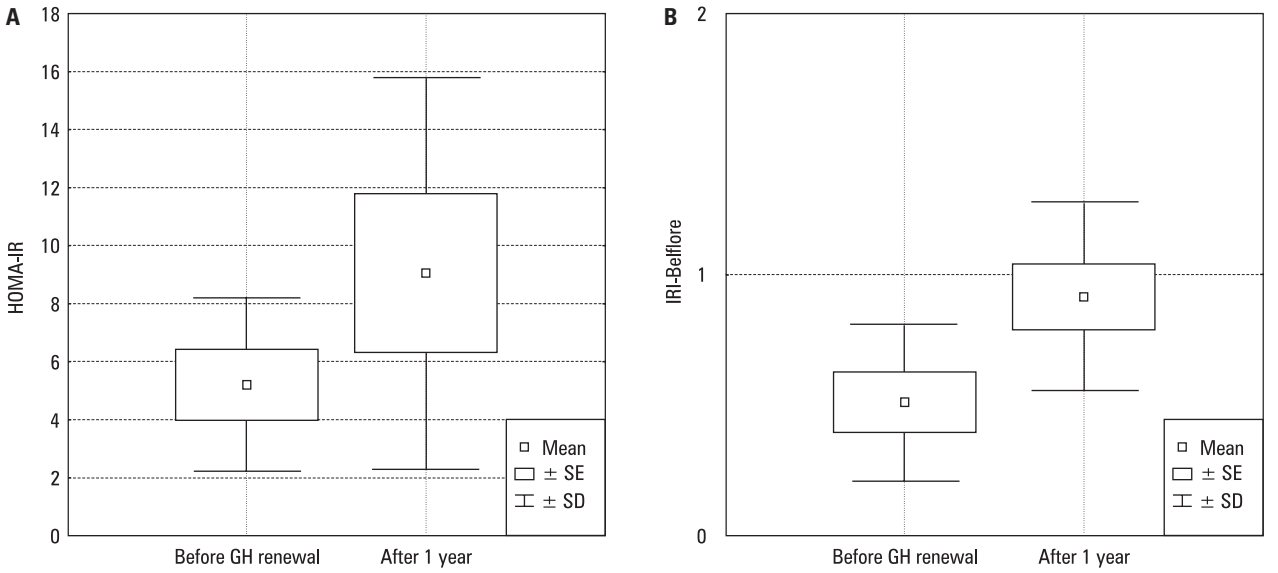

Figure 6A. *Comparison of HOMA insulin resistance index (HOMA-IR) before and after 1 year of renewed GH treatment.* ***B.*** *Comparison of insulin resistance index acc. to Belfiore (IRI-Belfiore) before and after 1 year of renewed GH treatment*

Rycina 6A. *Porównanie wskaźnika insulinooporności HOMA (HOMA-IR) przed i po roku ponownego leczenia GH.* ***B.*** *Porównanie wskaźnika insulinooporności według Belfiore (IRI-Belfiore) przed i po roku ponownego leczenia GH*

crease in LDL-Ch and an insignificant decrease in TCh was observed. In most trials [22–25], a reduction in TCh and LDL-Ch was reported with no significant effect on HDL-Ch and TG levels. In younger patients, however, the initial lipid parameters presented as either normal or less disturbed [21] compared to older patients [20]. The above-mentioned observations indicate a worsening lipid metabolism in adult patients with untreated severe GHD, while the improvement of lipid profile during low-dose GH therapy in young adults with severe GHD speaks for the necessity of continuation of the therapy after completion of growth promotion.

There is no doubt that at the moment of final height achievement, bone mass accrual is still not complete. Thus, GH therapy withdrawal in the patient with severe GHD at that time point leads to a reduction in peak bone mass. The legitimacy for GH therapy continuation in young adults at final height has recently been accepted [10, 11]. It was even proposed in Consensus guidelines from 2007 [11] that GH secretion be reassessed twice: once just after completion of linear growing and, in selected cases, for a second time after completion of somatic growth, at the age of approximately 25 years. Moreover, the cut-off value of GH peak in ITT in the transition period (in first re-evaluation) was recommended at the level of 6 ng/ml. Different cut-off values for the arginine-GHRH test, with respect to the patient's BMI, were also suggested, with higher cut-off levels for lean patients (11 ng/ml) than for obese patients (8 ng/ml for BMI 25–30 kg/m^2 and 4 ng/ml for BMI over 30 kg/m^2) [11]. Retrospective analysis of our group showed that all the 41 patients with non-confirmed PSGHDA had GH peak in ITT over 6.0 ng/ml. Among them, GH peak in the arginine-GHRH test ranged from 10.4 ng/ml to over 40.0 ng/ml, although remaining within the normal range according to the modified criteria of test interpretation.

The positive effect of GH replacement on QoL in adults with severe GHD is unquestionable [21]. A worsening of QoL after completion of growth-promoting GH therapy was reported by most of our patients, and the considerable improvement of QoL was confirmed by the scores of QoL-AGHDA. Interestingly, QoL presented a decrease even in young adults with no severe metabolic abnormalities and after a relatively short period of GH therapy discontinuation.

Neither our results nor any from previous studies [21, 22, 26–28] report severe adverse effects of low-dose GH therapy, including disturbances in glucose metabolism and insulin resistance. However, the unfavourable effect on insulin sensitivity should be taken into account during GH administration. According to our results, it seems that OGTT with calculation of IRI-Belfiore allows earlier detection of increased insulin resistance than assessment of fasting glucose and insulin levels.

Conclusions

The observed positive effects on body composition, lipid metabolism and QoL, together with the absence of adverse events, confirm the indications to GH therapy in young adults with severe GHD.

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