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THE INFLUENCE OF GROWTH HORMONE TREATMENT ON INSULIN SENSITIVITY IN CHILDREN AND ADOLESCENTS

ÇOCUK VE ADOLESANLARDA BÜYÜME HORMONU TEDAVİSİNİN İNSÜLİN DUYARLILIĞI ÜZERİNE ETKİSİ

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ABSTRACT

Objective: It has been reported that long-term growth hormone (GH) treatment may impair insulin sensitivity, hepatic glucose production, and insulin-dependent glucose utilization. In our study, we examined the effects of GH treatment on insulin sensitivity in patients with GH deficiency after one year treatment.

Materials and Methods: Fifty-nine patients (22 female, 37 male) with GH deficiency who received GH therapy were included in this study. Anthropometric measurements and pubertal examination of the patients were done. Fasting plasma glucose (FPG), fasting plasma insulin (FPI), HbA1c levels were measured and oral glucose tolerance test (OGTT) (1.75 g/kg, max. 75 g) was performed before and one year after treatment. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and Matsuda indices were calculated.

Result: The mean age of the patients at the start of GH treatment was 11.6±2.6 years old. The height standard deviation score (SDS) of the patients was -2.5±0.7, and the body mass index (BMI) SDS was -0.2±1.2. After one year, height SDS was -1.8±1.0 and BMI SDS was similar compared to baseline measurements. No difference was found between the initial and first-year pubertal stages of the patients. At the end of the first year, FPG and HbA1c levels did not change. When baseline and the first year results were compared, FPI, peak insulin, and total in-

ÖZET

Amaç: Uzun dönem büyüme hormonu (BH) tedavisinin insülin duyarlılığını azaltabileceği, karaciğerde glukoz üretimi ve insülin bağımlı glukoz kullanımını bozabileceği bildirilmektedir. Çalışmamızda bir yıllık BH tedavisinin insülin duyarlılığı üzerine etkilerini incelemeyi amaçladık.

Gereç ve Yöntem: Çalışmaya BH eksikliği tanısı ile BH kullanan 59 hasta (22 kız, 37 erkek) dahil edildi. Antropometrik ölçümler ve puberte muayeneleri yapıldı. Tedavi öncesi ve tedavi sonrası birinci yılda plazma açlık glukoz (PAG), plazma açlık insülin (PAİ), HbA1c düzeyleri ölçüldü ve oral glukoz tolerans testi (OGTT) (1,75 g/kg maks 75 g) yapıldı. İnsülin Direncinin Homeostatik Modeli Değerlendirmesi (HOMA-IR) ve Matsuda indeksleri hesaplandı.

Bulgular: Tedavi öncesi hastaların ortalama yaşı (ort±SD) 11,6±2,6 yıl idi. Hastaların ortalama boy standart deviasyon skoru (SDS) değeri -2,5±0,7, vücut kitle indeksi (VKİ) -0,2±1,2 idi. Tedavi sonrası birinci yılda boy SDS -1,8±1,0, VKİ SDS başlangıç değerleri ile benzer idi. Tedavi öncesi ve sonrasında puberte evresi benzerdi. Birinci yıl sonunda PAG ve HbA1c düzeylerinde değişiklik saptanmadı. Tedavi öncesi ve tedavi sonrası karşılaştırıldığında, birinci yılda PAİ, zirve insülin ve toplam insülin düzeyleri anlamlı olarak daha yüksek idi (p=0,037; p=0,05; p=0,017). Matsuda indeks anlamlı olarak düşük saptandı (p=0,009). Tedavi

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sulin were significantly higher at the first year (p=0.037; p=0.05; p=0.017), and the Matsuda index was found to be significantly lower (p=0.009). While HOMA-IR was higher in the first year, the difference was not significant.

Conclusion: We observed that short-term GH treatment caused a decrease in insulin sensitivity, but did not reach disease-causing levels. It is important to monitor children receiving GH treatment for insulin resistance. We recommend further measurements of FPI and FPG, and performing OGTT to evaluate the degree of deterioration of glucose metabolism in risky patients.

Keywords: Growth hormone, glucose metabolism, insulin resistance, oral glucose tolerance test

sonrası HOMA-IR daha yüksek olmasına rağmen istatistiksel olarak anlamlı fark bulunmadı.

Sonuç: Çalışmamızın sonucunda, kısa dönem BH tedavisinin insülin duyarlılığında azalmaya sebep olduğunu ancak yine de hastalığa sebep olacak seviyelere ulaşmadığı sonucuna vardık. BH tedavisi alan hastaları insülin direnci açısından izlemek önemlidir. İzlem sırasında PAG ve PAİ ölçümü ve riskli hastalarda glukoz metabolizmasındaki bozulmaları belirlemek için OGTT yapılmasını önermekteyiz.

Anahtar Kelimeler: Büyüme hormonu, glukoz metabolizması, insülin direnci, oral glukoz tolerans testi

INTRODUCTION

Growth hormone (GH) has metabolic benefits on lipid profiles and body proportions and has favorable effects on bone metabolism. However, the influence of GH on glucose homeostasis is complex. It is known that GH has a direct negative effect on insulin sensitivity, and an indirect positive effect through insulin growth factor 1 (IGF-1), which has an insulin mimetic, glucose-lowering effect (1). The relationship between the GH/IGF-1 axis and insulin has not been clearly established yet.

The lipolytic effect of GH in the visceral and subcutaneous adipose tissue causes an increase in free fatty acids (FFA) (2). Increased FFA in circulation inhibits insulin receptor substrate-1 and phosphoinositide-3-kinase activation in skeletal muscle and the liver and impairs insulin mediated glucose uptake by skeletal muscle and induces insulin resistance (3). In addition, GH stimulates glucose production via glycogenolysis and gluconeogenesis in the liver and kidney (4,5).

Insulin growth factor 1 and insulin receptors have similar properties, and they can bind to their own receptor with great affinity and each other's receptor weakly. IGF-1 may cause hypoglycemia with a possible mechanism of stimulating glucose uptake by skeletal muscle and decreasing gluconeogenesis through insulin receptors and/or IGF-1 receptor activation which is shown *in vivo* studies (6,7).

In adults GH deficiency is associated with increased cardiovascular risk, increased abdominal obesity and hyperlipidemia, which may be a consequence of decreased IGF-1 levels. GH therapy seems to protect adults from hyperlipidemia and hypertension, however, careful monitoring of glucose metabolism is recommended (8,9). Moreover, the prevalence of diabetes is reported to be high in acromegalic patients who are known to have excess GH (5). Similarly, GH-treated children were reported to have an increased incidence of type 2 diabetes, and monitoring glucose metabolism in GH-treated patients who have an increased risk of diabetes is recommended (10,11). Studies in children and adolescents are limited in this issue and if insulin resistance will develop, it remains unknown in what year of treatment it will come out. We planned this study accordingly and we aimed to evaluate the effects of GH on glucose metabolism by comparing oral glucose tolerance test (OGTT) responses, before and one year after treatment in patients with idiopathic GH deficiency (GHD).

MATERIALS and METHODS

The study population included patients who were diagnosed with idiopathic GHD and received GH treatment. The study was designed as an observational study performed retrospectively, and the data was collected from patient files. The patients had short stature due to idiopathic GHD. Idiopathic GHD was diagnosed in children who had low growth velocity, with stimulated GH levels below 10 mg/L on GH stimulation tests (GHST), normal cranial and hypophysial magnetic resonance imaging, no other pituitary hormone deficiencies and no underlying reason for GHD (12,13). For GHST, clonidine (0.15 mg/m^2 per oral) and L-dopa (10 mg/kg per oral) tests were used. For each test, blood samples for GH levels were drawn at the baseline, 30, 60, 90, and 120 minutes. Peak GH values less than 10 mg/L were accepted as a low GH response (14,15).

Patients with idiopathic short stature and patients who have known syndromes like Turner syndrome, Prader-Willi syndrome etc., who have chronic disorders, use drugs other than GH, those born as small for gestational age (SGA) and who have a first-degree relative with diabetes were excluded from the study.

Anthropometric measurements were done by the same auxologist. Height was measured using a Harpenden stadiometer (nearest 0.1 mm) which was calibrated at intervals (Holtain Ltd., Crymych, UK). Weight was measured using a digital electronic scale (nearest 0.1 kg). Standard deviation score (SDS) calculations of height, weight, and body mass index (BMI) were done according to the national data of the measurements (16). Marshall and Tanner's staging was used to evaluate puberty (17,18). GH treatment was started subcutaneously daily before bedtime and all patients completed one year of treatment.

Each subject underwent an OGTT to assess insulin sensitivity and glucose tolerance. GH treatment was initiated in patients with a standard dose and individually adjusted according to maintain IGF-1 levels in normal ranges. OGTT, HbA1c, and c-peptide levels were measured before the start of GH treatment and one year after treatment. Each test was performed after 8 hours of overnight fasting. Immediately before the test, samples for fasting plasma insulin (FPI), fasting plasma glucose (FPG), c-peptide, and HbA1c were drawn. Each subject was given 1.75 g/kg oral glucose (max 75 g, 4g/1mL dilution with water) and then samples for insulin and glucose were taken at the baseline and 30, 60, 90, and 120 minutes after the glucose intake.

Glucose was measured by using standard laboratory methods. Insulin was measured with a chemiluminescent immunoassay. HbA1c was measured by ion-exchange high-performance liquid chromatography and the concentrations for insulin and IGF-1 were tested by using IMMULITE 2000 Xpi Analyzer (Siemens, India).

American Diabetes Association criteria were used to classify the glucose metabolism disorders. Diabetes was diagnosed with FPG higher than 126 mg/dL or 120-min glucose higher than 200 mg/dL or HbA1c ³6.5%. Glucose intolerance was defined as FPG levels between 100-126 mg/dL and/or 120 min glucose level of 140-200 mg/dL. FPI levels of ³15 mU/mL in prepubertal and ³20 mU/mL in pubertal children and insulin levels higher than 75 mU/mL at 120 min and total insulin above 300 mU/mL were considered as insulin resistance (19,20).

To estimate insulin sensitivity and total insulin, the homeostasis model assessment insulin resistance index (HOMA-IR), and Matsuda index were calculated from the results of OGTT. The Matsuda index was calculated before and one year after GH treatment based on the formula as described by Matsuda and DeFronzo (21): $10.000/\sqrt{FPG\ (mg/dL)} \times FPI\ (mU/mL) \times Glucose_{mean}\ (mg/dL) \times Insulin_{mean}\ (mU/mL)$. HOMA-IR was calculated as the Matthews formula FPI (mU/mL) x FPG (mg/dL)/405 (22).

The study was performed with the written informed consent of parents. The study protocol was approved by the local ethics committee of Istanbul University, Istanbul Faculty of Medicine (Date: 02.10.2020, No: 24) and conducted according to the Helsinki Declaration's ethical statement.

Table 1: Clinical and biochemical findings of patients

	Baseline mean±SD (median; ranges)	1st year mean±SD (median; ranges)	p value
Age, year	11.6±2.6 (12.2; 5.3-15.3)	13.1±2.5 (13.3; 6.6-17.3)	**<0.001**
Weight SDS	-1.4±1.1 (-1.5; -3.7-1.1)	-1.1±1.3 (-1.6; -3.1-2.1)	**<0.001**
Height SDS	-2.5±0.7 (-2.4; -4.3—1.2)	-1.8±1.0 (-1.9; -4.5-1.4)	**<0.001**
BMI SDS	-0.2±1.2 (-0.2; -2.2-2.2)	-0.2±1.3 (-0.5; -2.7-3.2)	0.964
Prepubertal n(%) **Pubertal n(%)**	16 (27.1) 43 (72.9)	11 (18.6) 48 (81.4)	0.380
IGF1 SDS	-1.0±1.1 (-1.0; -2.9-3.7)	-0.02±1.3 (-0.1;-2.1-3.9)	**<0.001**
OGTT			
FPG mg/dL	80.4±10.0 (80; 61-109)	82.1±9.1 (82; 60.1-110)	0.168
FPI mU/mL	13.6±7.9 (11.4; 2.3-36.2)	15.9±11.1 (14.2; 3.9-73)	**0.037**
2nd h glucose mg/dL	114.5±19.5 (111; 80-168)	114.4±24.0 (114; 72-226)	0.702
2nd h insulin mU/mL	71.8±51.9 (55.3; 16.1-288)	82.8±56.2 (73.7; 2.2-316)	**0.05**
Peak insulin mU/mL	107.1±68.5 (89.5;24.4-332)	126.2±77.1 (120.5;17.2-464)	**0.012**
Total insulin mU/mL	323.5±200.2 (278;34.9-914)	377.8±235.1 (341.4;26.5-1540)	**0.017**
c-peptide ng/mL	2.2±0.8 (2.2; 0.7-4.2)	2.3±0.9 (2.0; 1.0-4.9)	0.166
HbA1c %	5.3±0.3 (5.3; 4.6-6.0)	5.4±0.4 (5.5; 4.1-5.9)	0.126
HOMA-IR	2.7±1.6 (2.3; 0.3-8.0)	3.2±2.5 (2.7; 0.3-16.1)	0.064
Matsuda index	5.8±5.6 (4.2; 1.4-36.6)	5.6±8.2 (3.0; 0.6-56.1)	**0.009**

SD: Standard deviation score, BMI: Body mass index, IGF1: Insulin growth factor 1, OGTT: Oral glucose tolerance test, FPG: Fasting plasma glucose, FPI: Fasting plasma insulin, HOMA-IR: Homeostasis model assessment insulin resistance

Statistical analysis

Statistical analyses were made using the Statistical Package for Social Sciences (SPSS) program for Windows 22.0. The Shapiro-Wilk test was used to determine the distribution of variables. Results were presented as mean±SD and categorical variables were expressed as numbers or percentages, where appropriate. Comparisons of continuous variables between groups were performed with the Wilcoxon sign rank test for paired samples and those of categorical variables with the Fisher's exact test. Correlation analysis between groups was analyzed using Spearman's test. p-value <0.05 was accepted as statistically significant.

RESULTS

A total of 59 patients consisting of 22 females (37.3%) and 37 males (62.7%) participated in our study. The mean age of the patients at presentation was 11.6±2.6 years old (females 10.2±1.9 years old, males 12.5±2.6 years old). The clinical and biochemical characteristics of the patients are presented in Table 1. All patients were born at an appropriate weight according to gestational age. The mean height SDS was -2.5±0.7, weight SDS was -1.4±1.1, and BMI SDS was -0.2±1.2. When the puberty stage was classified according to five subgroups, statistical evaluation could not be done because some of the puberty groups were too small for evaluation. Therefore, we compared prepubertal patients with pubertal ones. At presentation 27.1% of the patients were prepubertal and 72.9% of the patients were pubertal. The baseline IGF-1 SDS was -1.0±1.1. The peak GH level of GHST was (mean±SD) 5.5±2.6 mg/L and (median; min-max) 6.0; 0.2-9.9 mg/L. Before treatment, FPG, FPI, HbA1c, and c-peptide levels were in normal ranges. HOMA-IR was 2.7±1.6 and Matsuda index was 5.8±5.6. As expected, after one year of treatment weight and height SDS improved significantly. However, no marked change was noted in BMI SDS. After one year 18.6% of the patients were prepubertal and 81.4% were pubertal and there was no significant difference between the initial and the first-year puberty stages of the patients (p=0.380). After GH treatment we noticed a significant increase in IGF-1 levels, however, it was still in normal ranges (p<0.001). At the end of the first year, FPG, HbA1c, and c-peptide levels were in normal ranges and did not change significantly in comparison to baseline values. First-year FPI was 15.9±11.1mU/mL, peak insulin level was 126.2±77.1mU/mL, total insulin level was 377.8±235.1mU/mL, and Matsuda index was 5.6±8.2. When the initial and the first-year results were compared, FPI, peak insulin, and total insulin levels were significantly increased after GH treatment (p=0.037; p=0.05; p=0.017); The Matsuda index was found to be significantly lower (p=0.009). Although first-year HOMA-IR levels (3.2±2.5) were higher than pretreatment levels (2.7±1.6), no differences were found between HOMA-IR levels among patients (p=0.064). FPG and 120 min glucose levels were within normal ranges before and after treatment and we did not detect type 2 diabetes in our patients.

DISCUSSION

In our study, we investigated the changes in glucose metabolism and insulin levels in patients with GH deficiency who received GH treatment. The GH effect was confirmed to maintain a positive response by the increase in height and IGF-1 SDS. In our patients, we found significantly higher insulin levels when compared to the levels at the start of therapy. Insulin levels and insulin indices revealed a decrease in insulin sensitivity and increased insulin resistance. However, we did not have any patients who developed diabetes in the follow-up and we did not observe a change in glucose levels.

GH treatment has been used since the 1990s for GH deficiency. Since then, there has been an increasing number of studies related to the effects and side effects of GH. Adults with GH deficiency have an increased risk of atherosclerosis, insulin resistance, deterioration in lipid profile, and increased risk for cardiovascular mortality (8,23). GH therapy provides an increase in muscle strength, lean mass, bone mineral density, and benefits for lipid metabolism. The risks of cerebrovascular disease and insulin resistance constitute the main limitations of GH therapy in adulthood (9).

Glucose intolerance following impaired insulin sensitivity and increased insulin resistance raises concerns about the possibility of developing diabetes during GH treatment in the long term. GH has an important role in glucose homeostasis and insulin metabolism, but the data about the metabolic effects of GH therapy in childhood is controversial. Some studies showed deterioration in insulin sensitivity with pubertal development and ageing progress (24,25). Moreover, GH treatment seems to be associated with impaired insulin sensitivity in the short term, and long-term studies suggested that this initial negative effect was temporary (26). However, Cutfield et al. reported the results of an international pharmacoepidemiological survey which indicates an increased incidence of diabetes mellitus and glucose intolerance in children and adolescents who receive GH therapy and have a predisposal factor for diabetes (10). This acceleration in diabetes development may be reversible after discontinuation of treatment or dose reduction. Lutski et al. found no difference in diabetes incidence among patients with idiopathic GH deficiency and those who were born with SGA and received GH therapy during childhood when compared with the healthy population (27). However, they advised checking glucose levels closely during and after treatment, especially for individuals with diabetes risk factors such as a family history of diabetes, obesity, and Turner syn-

drome. GH therapy in children with SGA seems to be safe in terms of carbohydrate metabolism. Because no adverse effect was detected in glucose metabolism of SGA children during 260 weeks of GH treatment and in another long follow-up study, glucose metabolism was found to be normal at the end of six years in short SGA children (28,29).

Most studies have demonstrated an increase in insulin levels and HOMA-IR and normal glucose levels after one year of treatment of GH in prepubertal and pubertal children with GH deficiency. Our first-year results are in line with the reported data. We summarized the studies investigating the one-year effects of GH therapy on glucose metabolism in Table 2 (30-37).

According to the results of long-term studies, GH treatment is well tolerated after a three year follow-up and does not impair glucose metabolism, although it causes an increase in insulin levels. This increase in insulin levels started after one year of treatment and did not increase in the following years (35). A six year follow-up study showed the safety of GH treatment on glucose metabolism in GH-deficient children and they attributed the increased insulin secretion to the fact that GH causes a positive influence on beta cell capacity (38). Another study revealed a significant worsening in insulin sensitivity after four years of GH treatment in GH deficient children, while glucose and HbA1c levels were normal (31). Some long-term studies have shown hyperglycemia and insulin resistance under GH therapy. Glucose intolerance has been found in children who consume a high amount of simple carbohydrates and who have bad dietary habits. They suggest evaluating the diets of children carefully because these effects are possibly reversible with appropriate diet and may not require discontinuation of treatment (39).

In a recent study in an animal model, although an increase in endogenous GH and a concomittant increase in IGF-1 and insulin were detected, insulin sensitivity remained normal and glucose tolerance improved under GH therapy. The increase in insulin levels without systemic insulin resistance in the body was thought to be a result of increased beta cell mass or function (40).

In pubertal children, a physiological increase in insulin secretion and decreased insulin sensitivity is a known condition (41). It is difficult to estimate the role of puberty in the changes in glucose homeostasis during GH therapy. Pubertal children who are treated with GH may have an increased risk for glucose intolerance. However, in our study increased insulin levels were detected both in pubertal and prepubertal children. Furthermore, the changes in insulin levels cannot be attributed to body weight, since BMI SDS did not change significantly during the treatment. Besides, the increased insulin levels may be a result of increased beta cell compensatory capacity that develops secondary to GH-mediated inhibition of glucose uptake in the muscles and liver.

The main limitation of the present study is to assess insulin resistance and beta cell function with OGTT. The hyperinsulinemic-euglycemic clamp is the gold standard procedure, However, today, it is rarely used due to its impracticality in clinical practice. Another limitation of our study was that there were very few patients in puberty subgroups. Therefore, the effects of puberty on insulin resistance could not be clearly evaluated.

Table 2: Effects of one year recombinant human GH treatment on glucose metabolism in children and adolescents with GH deficiency

Reference	n	Age	FPG (mg/dL)	FPI (μU/mL)	HOMA-IR	Findings
30	30	8.6±3.4	97.5±8.5	12.3±7.6	2.99±0.21	FPG↑, FPI↑, HOMA-IR↑
31	118	10.7±3.5	83.4±8.3	5.7 (2.8-9.5)	1.18 (0.54-2.07)	FPG↑
32	16	8.9 (3.4-14.7)	82 (68-85)	4.2 (0.27-14.3)	1.1 (0.45-2.12	FPG↑, FPI↑
33	34	11.6±2.6	86.9±6.2	17.5±11.3	3.7±2.4	FPG↔, FPI↑, HOMA-IR↑
34	73	10.5±2.8	4.9±0.5	9±6.1	2±1.4	FPG↔, FPI↔, HOMA-IR↑
35	101	10.4 (7.7-12.5)	82 (76-88)	7.9 (4.9-13.6)	1.16 (0.72-1.72)	FPI↑, HOMA-IR↑
36	30	9.3±0.5	85±1.8	7.7±1.2	1.7±0.4	FPG↔, FPI↑, HOMA-IR↑
37	30	9.84±1.48	85.1±7.7	10.6±8.9	1.6±0.62	FPG↔, FPI↔, HOMA-IR↑
This study	59	13.1±2.5	82.1±9.1	15.9±11.1	3.2±2.5	FPG↔, FPI↑, HOMA-IR↔

FPG: Fasting plasma glucose, FPI: Fasting plasma insulin, HOMA-IR: Homeostasis model assessment insulin resistance, ↔: No change in the values at the end of the study,↑: Increase in the values at the end of the study. The age of the patients was presented in mean±SD or range.

CONCLUSION

After one year of GH treatment, we demonstrated an increase in insulin resistance. However, this increase did not reach pathological levels. According to our results before starting GH treatment, checking FPI, FPG and HbA1c and in case of suspicious findings performing OGTT is a practical, easily applicable, and reliable method for evaluation of insulin resistance and glucose metabolism until new biomarkers are developed for this purpose in the following years. Our results do not exclude the possible development of glucose intolerance with long-term use of GH treatment and we suggest performing OGTT annually while using GH in children at risk and detecting metabolically affected children. Following up with patients after treatment discontinuation is important since insulin resistance can be reversible. In addition, studies with larger numbers of patients are needed to investigate the effects of puberty in children receiving GH treatment.

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