Research Article

Relationship between Leptin and Insulin-like Growth Factor-1 in Children and Adolescent with Growth Hormone Deficiency

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Date Submitted 12.5.2014:
Date Accepted:15.9.2014

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Abstract

Background: Growth hormone deficiency (GHD) is suspected in subjects with short stature (SS) and reduced growth velocity in whom other causes of poor growth have been excluded. Insulin-like growth factor-1 (IGF-1) measurements are relatively newer methods for evaluating GHD or GH adequacy.
Objective: To study the relation between levels of leptin and IGF-1 in the children and adolescents in whom GHD was found.
Patients and Methods: This study was conducted during the period from June 2013 until the end of March 2014. The patients were attending to the National Diabetic Center/ AL-Mustansiriya University. Serum IGF-1 and leptin were measured in children and adolescent with GHD; 56 children with GHD were participated in this study their age range was (5-17) years, they were compared with 30 healthy children as control group.
Results: Means BMI and basal serum levels of GH and IGF-1 were significantly decreased in children and adolescent with GHD when compared with the control group. There was a significant decrease in serum level of IGF-1 in boys with GHD as compared to girls with GHD, while there was no significant difference in basal GH and leptin between boys and girls with GHD. A significant negative correlation was found between leptin versus BMI and IGF-1 in both gender groups, while a significant positive correlation was found between serum IGF-1 versus BMI and GH in children with GHD.
Conclusions: The present results are consistent with the hypothesis that leptin could contribute to the regulation of GH secretion and IGF-1 concentrations.

Keywords: Growth hormone deficiency, IGF-1, leptin.

INTRODUCTION

Growth hormone deficiency (GHD) depends on the assumption that GH deficient children have a lower GH response to stimulation compared to that of normally growing children [1]; the biosynthesis of growth hormone (GH) from somatotrophs is stimulated through increased intracellular Ca^{2+} concentrations [2]. Growth hormone is a single chain, 191 amino acid protein of 22 kD molecular weight and it is produced by the anterior pituitary gland [3]. In addition, secretion of GH is consistently at a basal concentration. The GH pulsatility is mainly dominated by the hypothalamic hormones, growth hormone releasing hormone (GHRH), which stimulates GH secretion and somatostatin, which inhibits GH secretion [4].

Insulin-like growth factor-1 (IGF-1), a protein with 7.6 kD and 70 amino acids, has a 48% similarity with proinsulin [5]. About 99% of plasma IGF-1 circulates bound to IGF-binding protein-3 (IGFBP-3) and compose a large 150 kD complex that cannot leave the circulation; [6] thus, IGF-1 is reflective of circulating GH, and, in contrast to GH, vary relatively little through the course of the day and thus can be measured easily as a screening test for GHD [7]. The diagnosis of GHD in

conjunction with other pituitary defect and/or organic pathologies is generally straightforward [8]. Consistently, GHD may be eliminated in the patients, in whom both GH and IGF-1 secretion are normal [9]. Children with GHD have a slow rate of growth, usually less than 2 inches per year. The slow rate of growth may not appear until a child is 2 or 3 years old. They will be so shorter than most or all children of the same age and gender. The cause of GHD is mostly unknown. It may be congenital or develop as the result of an injury or medical condition. Severe brain injury may also cause GHD [10]. Short stature (SS) may be divided to familial or non-familial and may be with or without retardation of pubertal development [11]. Short stature in children due to GHD, chronic renal failure or Turner's syndrome is most often treated with human GH. Growth hormone is one of the most vastly used hormones in supplementation [12].

Besides GH, the nutritional status of the cell is a potent regulator of IGF-1 serum levels. After birth, IGF-1 concentrations rise in response to GH and increase steadily during childhood [13]. Malnutrition and variations in the GH/IGF axis seem to be the most frequent and most important factors contributing to the degree of growth disturbance [14].

Leptin is one of the most serious adipose derived hormones. Leptin is a 16 KDa protein hormone that plays a key role in regulating energy homeostasis [15]. Although the (GH/IGF) axis plays a substantial role in the regulation of body composition [16], circulating leptin levels initiate the body's energy homeostasis and neuroendocrine, immune as well as metabolic function [17].

The aim of the present study was to examine the relationship between leptin and IGF-1 levels in children and adolescent with GHD.

PATIENTS AND METHODS

This study was conducted during the period from June 2013 until the end of March 2014. The patients in this study were attending to National Diabetic Center/ AL-Mustansiriya University. Serum sample was collected for basal measurements of GH, IGF-1, and leptin in 56 children (30 boys and 26 girls) with GHD and compared with 30 healthy children (16 boys and 14 girls) as control group. Their age range was (5-17) years. Clonidine orally administrated was chosen to stimulate GH secretion [18].

Verbal consent was taken from the patients' family. All information was obtained directly by medical history in a private interview by the authors which includes family history. All subjects were not receiving GH or any medications that interfere with IGF-1 analyses. Also, subjects who had renal diseases, liver diseases, malignant disorders, diabetes mellitus, and diseases of the pituitary gland or thyroid gland, were excluded.

body mass index (BMI) criterion was chosen for both the studied and control group according to the centers for disease control and prevention (CDC) growth charts developed by the National Center for Health Statistic in collaboration with the National Center for Chronic Diseases Prevention and Health Promotion [19].

Serum leptin concentrations were measured by the DRG leptin ELISA kit [20]. Serum GH concentrations were determined by (IRMA- Immunotech, France) [21], and serum IGF-1 concentrations were determined by (IRMA- Immunotech, France) [22].

Data were analyzed using computer facility, the available statistical package of SPSS-17 (statistical packages for social science-version 17). Data were presented in simple measures of number, and means (±standard deviation [SD]). The significance of difference between quantitative variables was tested using t-test for comparing between two means of independent group. Statistical significance was set at $P<0.05$.

RESULT

Characteristics of GHD and control group were summarized in table (1). There was no significant difference in age between GHD patients and control group. Means of BMI, basal serum levels of GH and IGF-1 were significantly decreased in GHD patients when compared with the control group, while there was a significant increase in serum leptin and leptin/BMI ratio in GHD patients when compared with the control group, ($P<0.05$).

Table (2) showed biochemical characteristics in GHD group according to gender. There was a significant decrease in serum levels of IGF-1 in boys with GHD as compared to girls with GHD, ($P=0.01$). There was no significant difference in basal serum levels of GH and leptin between boys and girls with GHD.

Table (3) showed a significant negative correlation between serum leptin versus BMI and IGF-1 in both gender groups, while a significant positive correlation was found between IGF-1 versus BMI and GH in GHD group. There was no correlation observed between leptin versus age and GH in GHD group.

Table 1. Characteristics of GHD and control group

NS: not significant

Variables	GHD (n=56)	Control (n=30)	P Value
Age (years)	12.80±4.31	11.46±6.18	0.41 NS
Gender (Boys/Girls) n.	30/26	16/14	-
BMI (kg/m^2)	14.10±4.42	21.74±5.50	0.01
Basal GH (ng/ml)	0.40±0.30	1.44±0.18	0.045
IGF-1 (ng/ml)	126.20±7.60	183.45±2.60	0.001
Leptin (ng/ml)	9.47±3.80	5.81±4.18	0.01
Leptin/BMI ratio	0.67±0.03	0.26±1.03	0.045

Table 2. Biochemical characteristics in GHD according to gender

Variables	Boys with GHD (n=30)	Girls with GHD (n=26)	P Value
Basal GH (ng/ml)	0.30±0.20	0.50±0.21	0.33 NS
IGF-1 (ng/ml)	120.32±1.61	132.3±1.60	0.01
Leptin (ng/ml)	7.90±2.30	10.81±2.42	0.19 NS

NS: not significant

Table 3. The correlations between serum leptin and IGF-1 with different variables in GHD

Parameters	Correlation coefficient (r)
Leptin vs. Age	0.133 NS
Leptin vs. BMI	0.822**-
Leptin vs. GH	0.287 NS-
Leptin vs. IGF-1	-0.401*
IGF-1 vs. Age	0.141NS
IGF-1 vs. BMI	0.62**
IGF-1 vs. GH	0.432*

***P<0.05, **P<0.001, NS: not significant**

DISCUSSION

Serum IGF-1 concentrations are known to reflect tissue levels to some extent and they are used as surrogate markers of growth and therapeutic adequacy in subjects receiving GH therapy [23].

The results of this study indicated some findings pointing to an influence of BMI on GH/IGF-1 axis, which probably reflect the complexity of interactions between metabolic signals and the somatotropic axis. Short stature patients with low BMI might have a relative IGF-1 resistance, whereas those with normal BMI tend to be less GH-sensitive, which might suggest the need for different therapeutic strategies in these children [24]. Short patients are reported to have lower BMI as compared to healthy peers [25], which is in agreement with the present results and a reduced appetite has been proposed as a contributory factor, table (1).

In this study, there was a significant difference in BMI, basal serum levels of GH, IGF-1, and leptin between GHD children and the control group.

The findings of a decreased basal serum level of IGF-1 in GHD patients' peers to favor low BMI as compared to BMI in their controls, table (1). This finding might denote a BMI-dependence disturbance in GH/IGF-1 axis in GHD patients; this may be attributed to insufficiency in non GH-induced production of IGF-1 which is in agreement with the results of Bouhours-Nouet et al [26].

Miyakawa et al [27] found a decrease in BMI in GHD children as compared to acromegaly and normal subjects, but it was not significant.

There was a significant distinction in IGF-1 levels observed through genders which are consistent with the study of Leite et al [28], table (2).

Previous study has also indicated that leptin secretion is affected by many hormonal and metabolic factors. Besides a close correlation to BMI, leptin secretion has been proposed to be modulated by insulin, thyroid hormones and supply of dietary energy [29].

In humans, a negative relationship between circulating leptin and GH secretion. Although the mechanism by which leptin and GH are inversely related has not been determined. Leptin may inhibit GH secretion or GH may inhibit leptin secretion and multiple regression analysis demonstrated that serum leptin levels were negatively associated with IGF-1 [30]. The present study also showed that there was a negative correlation between serum leptin and IGF-1 levels, table (3).

Leptin concentrations have been reported to be significantly higher in GHD patients compared with healthy controls [31]. In this study, leptin concentrations were in line with those observed in Kim et al study.

The possible explanations of the mechanisms of increased leptin concentrations in GH deficiency include the direct effect of GH and IGF-1 on leptin regulation of adipocytes [32].

Higher leptin levels in girls than in boys have previously been reported in children [33], which is in agreement with the present results, table (2).

Higher leptin levels in girls as compared to boys due to the fact that leptin levels in humans are also affected by sex steroid levels [34].

In this study, leptin resistance, which is represented by leptin/BMI ratio, also may contribute to the regulation of GH and IGF-1 concentrations.

Conclusions: This study hypothesized decreased levels of GH and IGF-1 in GHD children also found that leptin is increased in GHD children. These results may reflect the influence of several factors which could affect GH and IGF-1 levels, due to differences between subjects with respect to genetic background or nutritional status.

Acknowledgements:The authors thank Dr. Maan Abdul-jaleel Abdul-hadi and Dr. Ali Ibrahim for their assistance.

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