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Association between lipid profile and other biochemical parameters with growth hormone in children and adolescents with short stature

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ABSTRACT

Short stature is a general term that usually accompanies a lack of growth hormone among people, and is more common among children. In this study, some kidney functions and lipid profile tests were evaluated in children and adolescents with short stature to find any relationship between the disturbance in these parameters and the etiology of short stature. A total of 60 short stature patients with a growth hormone deficiency, age range between 4-18 years, along with 60 age-matched healthy volunteers, were included in this study. Serum levels of GH, IGF-1, urea, and creatinine, as well as lipid profile, were determined, and then statistical analysis was performed on the collected data. The obtained results indicated a significant decrease in serum levels of GH and IGF-1 ($p < 0.01$) in patients compared to control values. The results also indicated a substantial increase in serum levels of triglycerides and VLDL, mainly seen in children, and reported non-significant differences in HDL, LDL, and urea levels for GHD patients compared to control values. Additionally, the results showed a significant increase in the creatinine level of adolescent patients only. This study concluded that there is a clear relationship between disturbances in creatinine levels and the promotion of GHD in short stature patients. Current work has demonstrated that anomalies in the lipid profile, especially triglycerides and VLDL, are closely related to the causes of short stature. Finally, and most importantly, we can suggest that triglycerides and VLDL may help identify patients at an early age who are at risk of short stature, especially children.

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INTRODUCTION

Growth hormone (GH), also called somatotropin, is a peptide hormone that is important for human development. It is responsible for stimulating growth, cell proliferation, and cell regeneration. The growth hormone also stimulates IGF-1 production and increases the concentration of glucose and free fatty acids (Ranabir and Reetu, 2011; Greenwood and Landon, 1966). Insulin-like growth factor 1 (IGF-1), also called somatomedin C, is a peptide hormone that plays a vital role in childhood development and has anabolic effects in adults. IGF-1 is produced mainly by the liver and is character-

ized by similarities in the molecular structure of insulin (Höppener *et al.*, 1985; Ewaid and Abed, 2017).

Growth hormone deficiency (GHD) is a medical condition due to a lack of growth hormone if it begins in childhood or infancy, and is characterized by several symptoms, especially short stature. The cause of this condition is unknown in 75 percent of patients, and in most cases, brain malformations occur (Rikken *et al.*, 1995; Salim and Abed, 2017). GHD may be isolated or combined with other anterior and/or posterior hormonal deficiencies. GHD has been found to be a rare but important cause of short stature in children (Dattani and Malhotra, 2019). The incidence of congenital GHD with male predominance is 1 out of 4000 to 1 out of 10,000 live births (Kautsar *et al.*, 2019; Salim and Abed, 2019; Abed and Salim, 2019).

Short stature is a term used for a child whose length is two standard deviation more or below the mean for children of that sex and age (Rogol, 2016). In fact, short stature is a common problem in children, and it may occur due to many causes such as genetic, environmental, or chronic diseases. Diagnosis of short stature can be accomplished in two concerted ways, physical examination and laboratory testing. Treatment for short stature mainly depends on the correct diagnosis and the causative agent (Albalawi *et al.*, 2018).

The most important effect of growth hormone administration in humans is a marked increase in free fatty acids that influence the stimulation of lipolysis and ketogenesis after 1-2 hours. This stimulation constitutes a major physiological adaptation of stress and fasting (Møller *et al.*, 2003). GHD has shown an increase in triglycerides and cholesterol (mostly LDL cholesterol). In fact, treatment for GH in children with GHD demonstrated unclear changes in cholesterol concentration (Cuneo *et al.*, 1992; Abed and Salim, 2018).

It has been reported that both GH and IGF-1 reduce hepatic ureagenesis and gene expression of urea cycle enzymes. These findings strongly suggest that GH and IGF-1, at least in part, have exercised their influence on the regulation of urea synthesis at the gene level, and this is necessary for the anabolic effects of GH and IGF-1 (Grøfte *et al.*, 1997). In addition, GH can alter the level of creatinine in the blood by its anabolic effects on the muscles (Davani-Davari *et al.*, 2019).

Growth hormone is one of the most potent anabolic agents. A previous study investigated the effect of GH on the concentration of urinary creatinine over a 24-hour period as an indication of muscle mass catabolism in burned patients. GH is effective in reducing creatinine excretion in the urine. It has been speculated that this lack of creatinine excretion in the urine may be associated with muscle catabolism (Akçay *et al.*, 2001). Growth hormone and insulin-like growth factor-I are two important physiological regulators for growth, body composition, and kidney function. The disorder of the GH-IGF-1 axis is responsible for many important complications that appear in chronic kidney diseases (CKD), such as growth retardation and cachexia (Mak *et al.*, 2008). In animals, anterior pituitary insufficiency causes decreased GFR, and it was found that this phenomenon is reversible after the administration of GH. In patients with hypophysectomized, when a substitutive therapy is given for all hormones in the pituitary gland, GFR will decline without any parallel change in the extracellular size (Grunenwald *et al.*, 2011).

Currently, the diagnosis of growth hormone deficiency is based on clinical, biochemical, and neuroradiological studies. The Clonidine Test (CT) is widely used to assess the state of growth hormone secretion (Ibba *et al.*, 2018). To confirm GHD, provocative tests of GH secretion using psychological/pharmacological stimuli are required. In this work, the relationship between the expected disturbance in lipid profile and other parameters such as urea and creatinine on the etiology of short stature in children and adolescents were studied.

MATERIALS AND METHODS

Subjects and study design

This study includes one hundred and twenty subjects from children to adolescents with an age range between (4-18) years. Among them were sixty healthy individuals as a control group, male and female, and sixty short stature patients with growth hormone deficiency.

These subjects were selected from outpatients who were attended to the Pediatric department/National Diabetic Center (NDC)/Mustansiriyah University, Baghdad, Iraq.

The patients were diagnosed by an endocrinology specialist as a short stature with growth hormone deficiency.

Sample Collection

From each individual, 10 ml of blood was drawn through a vein puncture using disposable syringes and collected in a gel tube. Blood samples were collected from each subject between 8-11 a.m. after overnight fasting. After collection, the blood samples were centrifuged at 3000 rpm for 10 minutes.

Table 1: Anthropometricmeasurement of GHD patients and control groups

Anthropometric measurements	Mean ± SD		p -value
	Patients	**Control**	
Age (year)			
Children	8.40 ± 2.48	8.48 ± 2.66	0.901 NS
Adolescents	13.83 ± 1.08	14.30 ± 1.62	0.195 NS
Total	11.12 ± 3.33	11.39 ± 3.65	0. 668 NS
Weight (kg)			
Children	18.40 ± 4.09	23.66 ± 4.21	0.001**
Adolescents	37.06 ± 8.90	43.90 ± 7.78	0.002**
Total	27.73 ± 11.65	33.78 ± 11.94	0.006**
Height (cm)			
Children	109.93 ± 10.47	120.00 ± 10.04	0.001**
Adolescents	135.11 ± 10.72	149.00 ± 9.24	0.001**
Total	122.52 ± 16.48	134.50 ± 17.47	0.001**
BMI (kg/m2)			
Children	15.20 ± 2.58	16.53 ± 0.97	0.01*
Adolescents	20.04 ± 2.87	19.69 ± 1.43	0.549NS
Total	17.62 ± 3.63	18.11 ± 2.00	0.365NS

** (P<0.01), NS: Non-Significant.

Table 2: Distribution of studied subjects according to BMI Percentile

BMI Categories	Patients		Control	
	No.	%	No.	%
Underweight	12	20	2	3.3
Normal Weight	38	63.3	58	96.7
Overweight	7	11.7	0	0
Obese	3	5	0	0
Total	60	100	60	100

The resulting serum was stored at -20 °C until the time of analysis. Samples were analyzed at the National Center for Diabetes and Endocrinology at Mustansiriyah University.

Sample Analysis

The body mass index (BMI) was calculated from the subjects studied by the following formula: BMI = weight (kg) / length (m^2)

BMI Percentiles assort the position of an individual by indicating the percentage of the reference population that the individual is equal to or exceeds. The BMI percentile can be calculated via a BMI calculator or by a growth chart represented previously (Walker *et al.*, 2002). The BMI was categorized based on age- and sex-specific values of the 2,000 Centers for Disease Control and Prevention (CDC) growth charts. The categories were underweight (<5th percentile), normal weight (5th to 84th percentile), overweight (85th to 94th percentile), and obese (≥95th percentile) (Barlow, 2007).

Serum GH and IGF-1 levels were estimated by a sandwich chemiluminescence immunoassay (CLIA) following the protocol of the available kits supplied by (DiaSorin/Italy). Levels of lipid profile (cholesterol, triglyceride, and HDL), creatinine, and urea were estimated enzymatically using the colorimetric assay following the protocol of the available kits supplied by BIOLABO/France. Levels of LDL and VLDL were calculated according to the Friedewald equation.

Statistical analysis

Data was analyzed using SPSS statistical software, version 26. Independent-Samples Student t-test was performed between patients and control groups, and the resulting values were expressed as mean ± standard deviation (SD). The Pearson correlation coefficient was also carried out to determine the relationships between all study variables.

Table 3: Levels of GH and IGF-1 for patients and control groups.

Parameters	Mean ± SD		p-value
	Patients	**Control**	
Basal GH (ng/ml)			
Children	0.53 ± 0.19	0.60 ± 0.18	0.132 NS
Adolescents	0.52 ± 0.22	0.56 ± 0.19	0.553 NS
Total	0.53 ± 0.20	0.58 ± 0.19	0.144 NS
GH (ng/ml) after 1 hr.			
Children	2.59 ± 1.43	14.26 ± 3.12	0.001**
Adolescents	3.02 ± 1.72	15.81 ± 5.13	0.001**
Total	2.81 ± 1.58	15.03 ± 4.28	0.001 **
GH (ng/ml) after 1.30 hr.			
Children	1.44 ± 0.90	7.40 ± 3.42	0.001 **
Adolescents	1.51 ± 1.27	7.03 ± 3.07	0.001 **
Total	1.48 ± 1.09	7.22 ± 3.23	0.001 **
IGF-1 (ng/ml)			
Children	82.71 ± 32.59	208.50 ± 58.17	0.001 **
Adolescents	174.08 ± 85.79	258.80 ± 113.68	0.002 **
Total	128.40 ± 79.13	233.65 ± 93.05	0.001 **

** (P<0.01), NS: Non-Significant.

The statistical tests were significant at p<0.05 and highly significant at p<0.01 with a confidence interval of 95%.

RESULTS AND DISCUSSION

All anthropometric data obtained from patients with growth hormone deficiency and the control group are summarized in Table 1. The results showed a highly significant decrease (p<0.01) in the mean values of patients weight and length (27.73 ± 11.65 kg, 122.52 ± 16.48 cm) compared to the control values (33.78 ± 11.94 kg, 134.50 ± 17.47 cm). Additionally, BMI results revealed a non-significant difference (p>0.05) between patients (17.62 ± 3.63 kg/m^2) and control groups (18.11 ± 2.00 kg/m^2).

The results revealed that the study cases, both for children and adolescents, were in the same age range, and this is very important to give a real comparison between patients and control groups. The results obtained in this study are consistent with the results of a previous study (Ece *et al.*, 2014), which stated that the weight was lower in patients with a growth hormone deficiency, both children and adolescents, compared to the control group. However, the results are not consistent with the results of another study (Wang *et al.*, 2019). Differences between studies can be due to differences in nutritional status, sample size, and lifestyle of the subjects. Likewise, a previous study (Bahrani *et al.*, 2011) identified a significant decrease in the height of children and adolescents with growth hormone deficiency compared to the control group. This result is because GHD is one of the reasons for short stature that affect bone maturation (Olney, 2003). The current BMI results are consistent with the results of a previous study (Lee *et al.*, 2013) that reported non-significant differences in BMI between patients and the control group. This finding could be due to the fact that the BMI includes weight and height, and both of these are almost decreasing in the same range for both studied groups.

BMI percentile results showed a significant difference between patients and control groups, as shown in Table 2. The results are consistent with a previous study (Mikki *et al.*, 2009)that stated that some GHD patients were underweight. This finding may be due to factors such as malnutrition, socioeconomic status, and patient gender (Tzanela *et al.*, 2010). On the other hand, the reason for the high number of overweight cases in patients may be that GH has a lipolytic effect on adipose tissue, and patients with GH deficiency generally have abundant fat tissue. The current results are in good agreement with a previous study (Lee *et al.*, 2013), which has shown that secretion of GH decreases in obese people, and both spontaneous and stimulated GH levels are low in patients with GH deficiency.

The data in Table 3 shows the levels of GH and IGF-1 in the studied groups for children, adolescents, and total. A non-significant difference (p>0.05) was found in basal GH between patients (0.53 ± 0.20 ng/ml) and control (0.58 ± 0.19 ng/ml).

Table 4: Levels of biochemical parameters in GHD patientsand control groups

Parameters	Mean ± SD		p-value
	Patients	**Control**	
Cholesterol (mg/ml)			
Children	161.46 ± 21.75	150.46 ± 32.71	0.131 NS
Adolescents	161.93±23.07	156.63±29.12	0.438 NS
Total	161.70 ± 22.23	153.55 ± 30.86	0.100 NS
Triglyceride (mg/ml)			
Children	86.50 ± 6.99	78.83 ± 5.83	0.001**
Adolescents	90.90 ± 2.74	92.06 ± 8.22	0.464 NS
Total	88.70 ± 5.71	84.45 ± 9.72	0.025 *
HDL (mg/ml)			
Children	53.10 ± 5.20	52.90 ± 5.47	0.885 NS
Adolescents	51.63 ± 5.73	53.10 ± 5.16	0.303 NS
Total	52.36 ± 5.48	53.00 ± 5.28	0.520 NS
LDL (mg/ml)			
Children	91.06 ± 23.41	81.80 ± 32.18	0.207 NS
Adolescents	92.12 ± 24.85	85.12 ± 30.82	0.337 NS
Total	91.59 ± 23.94	83.46 ± 31.29	0.113 NS
VLDL (mg/ml)			
Children	17.30 ± 1.39	15.76 ± 1.16	0.001**
Adolescents	18.18 ± 0.54	18.41 ± 1.64	0.464 NS
Total	17.74 ± 1.14	16.09 ± 1.94	0.027 *
B. urea (mg/dl)			
Children	26.06 ± 3.78	25.90 ± 3.58	0.862 NS
Adolescents	27.70 ± 4.47	28.83 ± 3.81	0.295 NS
Total	26.88 ± 4.19	27.36 ± 3.95	0.517 NS
S. creatinine (mg/dl)			
Children	0.70 ± 0.20	0.74 ± 0.18	0.424 NS
Adolescents	0.87 ± 0.24	0.71 ± 0.20	0.007 **
Total	0.79 ± 0.24	0.72 ± 0.19	0.124 NS

** (p<0.01), * (p<0.05), NS: Non-Significant.

Table 5: Correlations between variables in the GHDpatients group (R-value)

variable	GH	GH2	GH3	IGF-1	TC	TG	HDL	LDL	VLDL	Urea	Creatinine
GH	1	.469**	.601**	.052	.291*	-.005	-.147	.304*	-.005	.179	.091
GH2	.469**	1	.647**	.151	.047	-.003	.095	.022	-.003	.082	.309*
GH3	.601**	.647**	1	.018	.267*	.032	-.045	.257*	.032	.199	.190
IGF-1	.052	.151	.018	1	.012	.215	-.205	.048	.215	.260*	.213
TC	.291*	.047	.267*	.012	1	.008	-.203	.975**	.008	.025	.075
TG	-.005	-.003	.032	.215	.008	1	-.104	-.017	1.000**	.146	-.102
HDL	-.147	.095	-.045	-.205	-.203	-.104	1	-.412**	-.104	.087	.067
LDL	.304*	.022	.257*	.048	.975**	-.017	-.412**	1	-.017	-.004	.038
VLDL	-.005	-.003	.032	.215	.008	1.000**	-.104	-.017	1	.146	-.102
Urea	.179	.082	.199	.260*	.025	.146	.087	-.004	.146	1	.143
Creatinine	091	.309*	.190	.213	.075	-.102	.157	.038	-.102	.143	1

**Correlationis significant at the 0.01 level
*Correlationis significant at the 0.05 level

While GH levels were found after 1 hour and 1.5 hours (provocation with clonidine) decreased significantly ($p<0.01$) in patients (2.81 ± 1.58 ng/ml) and (1.48 ± 1.09 ng/ml) compared to control values (15.03 ± 4.28 ng/ml) and (7.22 ± 3.23 ng/ml), respectively. The results revealed that IGF-1 levels were significantly reduced ($p<0.01$) in patients (128.40 ± 79.13 ng/ml) compared to control (233.65 ± 93.05 ng/ml). For details of the results of all children and adolescents, refer to Table 3.

The results presented here are consistent with a previous investigation (Bhagwat *et al.*, 2018) that reported a non-significant difference between basal GH levels in patients and control. It may be due to the release of growth hormone, which is pulsated with diurnal variation, under a negative feedback autoregulation loop, and may be affected by various factors. Factors that affect the secretion of growth hormone include sleep, exercise, and physical stress such as fasting, hypoglycemia, hyperglycemia, and shock. Growth hormone secretion shows the differences between sexes, with pulsatile male secretion versus continuous female secretion. Moreover, the level of secretion also decreases with age, a phenomenon called somatopause (Lim and Khoo, 2017; Ewaid *et al.*, 2020).

Current results for levels of GH2 (after 1 hr.) and GH3 (after 1.5 hr.) correspond to the results reported in a previous study (Bhagwat *et al.*, 2018). It may be due to the pulsatile way of GH secretion and the increase after the stimulation. Furthermore, the results of IGF-1 levels were consistent with a previous study (Bahrani *et al.*, 2011; Al-Zaidy *et al.*, 2019) who reported a significant reduction in IGF-1 levels among patients compared to healthy controls. It may be due to IGF-1 is a reliable marker of GH action and is affected by several factors such as age, gender, liver disease, and fasting state (Ewaid and Al-Ansari, 2019; Ewaid *et al.*, 2019; Mukherjee and Shalet, 2009).

Collective results describing the total values of the measured parameters for the two study groups are summarized in Table 4. The results confirmed that there were no significant differences ($p>0.05$) in the HDL level (52.36 ± 5.48 mg/dL) of GHD patients comparing with the control values (53.00 ± 5.28 mg/dL). While, there were a significant increased ($p<0.05$) in triglyceride level of patients (88.70 ± 5.71 mg/dL) compared to the control (85.45 ± 9.72 mg/dL). This increase appears very clearly in children, while there is no difference in adolescents. Refer to Table 4. Furthermore, the results showed a non-significant increase ($p>0.05$) in LDL levels (91.59 ± 23.94 mg/dL) and cholesterol levels (161.70 ± 22.23 mg/dL) of patients compared to the control (83.46 ± 31.29 mg/dL) and (153.55 ± 30.86 mg/dL), respectively. There was a significant increase ($p<0.05$) in VLDL levels in patients (17.74 ± 1.14 mg/dL) compared to control (16.09 ± 1.94 mg/dL), and it specifically appears in children. In addition, there were non-significant differences ($p>0.05$) in urea and creatinine levels between patients (26.88 ± 4.19 mg/dL, 0.79 ± 0.24 mg/dL) and control values (27.36 ± 3.95 mg/dL, 0.72 ± 0.19 mg/dL), respectively, bearing in mind that there is a significant increase in creatinine level of adolescents patients.

The results obtained in this study are consistent with previously reported results (Stawerska *et al.*, 2017), which showed non-significant differences in cholesterol and HDL levels and a significant increase in triglyceride and VLDL levels in patients with growth hormone deficiency compared to control. While the results disagree with the results of another study (Evans *et al.*, 2000) that stated there were no differences in lipid profiles between GHD and controls. Regarding urea and creatinine levels, the current results are consistent with a previous study (Ece *et al.*, 2014) that reported non-significant differences in urea and creatinine levels between GHD patients and control. Short stature is common in children with chronic renal insufficiency (CRI), and several reasons contribute to the pathogenesis including metabolic acidosis, water-electrolyte disturbances, protein malnutrition, and malnutrition with corticosteroid which create resistance to the action of GH (Abed and Salim, 2018; Hardin, 2008).

The correlation between all variables included in the current study was examined for GHD patients using Pearson correlation analysis, and the results were represented in Table 5. The results showed that the GH level was positively correlated with cholesterol and LDL levels. The analysis also revealed the presence of a positive correlation between the levels of GH and creatinine, especially in adolescent patients. Furthermore, the current study revealed a positive correlation of IGF-1 with urea levels.

The results showed a positive correlation between the levels of cholesterol and LDL and a positive correlation between the levels of TG with VLDL of patients with GHD. It also showed a negative correlation between the levels of LDL and HDL.

CONCLUSION

Valuable information is available on kidney function and lipid profile, but its association with short stature disorder needs further study. This study

shows a clear relationship between disturbances in creatinine and the promotion of GHD in short stature patients. The results indicated that serum creatinine level, more precisely in adolescents of GHD patients, is substantially affected relative to those in healthy subjects.

Current work has demonstrated that abnormalities in the lipid profile (especially triglycerides and VLDL) are closely associated with the etiology of short stature. Pearson correlation analysis revealed this demonstration, especially in children. Finally and most importantly, the results confirm that triglycerides in the blood and VLDL may help identify patients at an early age who are at risk of short stature (particularly children). More studies are recommended to understand the exact mechanism of the relationship between the lipid profile and creatinine with the short stature etiology.

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Conflict of Interest

None.

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