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Effect of Puberty and Gender on Metabolic Hormones Level and Lipid Profile in Patients with Growth Hormone Deficiency

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Abstract

The current study aims to evaluate the effect of puberty and gender on metabolic hormones level and lipid profile in a sample with growth hormone deficiency (GHD). Seventy-five Iraqi patients with GHD (45 boys and 30 girls) within the age range (3-15) years were involved in this study. The study was achieved in the National Diabetic Center for Treatment and Research /Al-Mustansiriya University in a period of October, 2018 to April, 2019.

Blood samples were obtained from the patients to determine the level of basal GH before stimulation with clonidine, GH_2 and GH_3 after 1 h. and 1.30 h. stimulation with clonidine, respectively; insulin-like growth factor-1 (IGF-1); level of metabolic hormones [thyroid hormones: triiodothyronine (T3), tetraiodothyronine (thyroxin) (T4), thyroid stimulating hormone (TSH), and cortisol]; and lipid profile [cholesterol, triglycerides (TGs), high density lipoprotein (HDL), low density lipoprotein (LDL) and very low density lipoprotein (VLDL)].

Effects of the puberty on the studied parameters revealed that the levels of GH_2, IGF-1, TGs and VLDL were significantly ($P<0.05$) higher in the pubertal group than the pre-pubertal group, while levels of T3 and T4 were significantly ($P<0.01$) lower in the pubertal group compared to the per-pubertal group. Non-significant ($P>0.05$) differences were found in level of other parameters (GH, GH_3, TSH, cortisol, cholesterol, HDL and LDL) between the two groups. Effect of gender on the studied parameters showed non-significant ($P>0.05$) differences between boys and girls.

It can be concluded from this study that puberty effects on some parameters such as GH2, IGF-1, T3, T4, TGs and VLDL in patients with GHD; while gender shows no significant effect on the all studied parameters.

Keywords: Growth hormone deficiency, metabolic hormones, puberty, gender.

Introduction

Growth hormone (GH), is known as somatotropin, it's a peptide hormone that secreted from the anterior pituitary and consists of 191 amino acid, 22,129 KDa single-chain protein with 2 bridges of di- sulfide. It has a central role in regulating postnatal growth and

metabolism and has pleiotropic effects on different human tissues; GH levels increase steadily during childhood and peak during the growth spurt in puberty [1].

Growth hormone deficiency (GHD) results when the pituitary gland does not produce enough growth hormone to stimulate the body to grow and develop in early and later childhood as a slow or flat rate of growth [2]. Children with GHD typically have typical body proportions, but are often shorter and shorter than their age compared to peers of the same age and gender [3]. Provocative GH testing continues to play a primary role in the diagnosis of GHD; the most common provocative agents include insulin, glucagon, clonidine, arginine, L-dopa, sleeping, fasting and heavy exercises [4].

Insulin-like growth factor-1 (IGF-1) is a polypeptide hormone structurally similar to insulin with endocrine, paracrine, and autocrine effects [5]. It is mainly produced by the liver and it is central to the somatotropic axis, acting downstream of GH [6].

The anabolic and metabolic effects of GH are affected by the thyroid hormones by increases the pituitary synthesis of this protein hormone [7]. The thyroid gland is one of the biggest organs in the body [8], its function is the production of thyroid hormones called triiodothyronine (T3) and thyroxine (T4) [9]. Thyroid stimulating hormone (TSH) modulates the production of hormones by the thyroid gland [10]. Also, GHD is induced by cortisol which is synthesized from cholesterol, is the main glucocorticoid in the zona fasciculate of human adrenal cortex [11]. Excess cortisol inhibits growth hormone secretion and the skeleton development [12].

Lipoproteins are complex particles with a central hydrophobic center of non-polar lipids, cholesterol and triglycerides that are insoluble in water and must therefore be transported together with proteins [13]. High density lipoproteins (HDL) these particles play a major role in the reverse transport of cholesterol from peripheral tissues to the liver. Low density lipoproteins (LDL) these particles are

derived from VLDL and IDL particles and are enriched in cholesterol even further. Very low-density lipoproteins (VLDL) these molecules are made from the liver and are full with triglycerides [14]. The deficiency of GH causes increased abdominal fat, unusual carbohydrate and lipid metabolism, because GHD suppress the activation of a critical enzyme for lipolysis which called hormone-sensitive lipase (HSL) [15].

Materials and Methods

Seventy-five Iraqi patients with GHD (45 boys and 30 girls) within the age range (3-15) years were involved in this study during their presence in the National Diabetic Center for Treatment and Research

/Al-Mustansiriya University.

Collection of blood samples

About (5 ml) of a venous blood specimen was taken from each patient after an overnight fasting, the specimen was kept in a clean dry gel tube and held to clot, they were centrifuged for 10 min at (3000 rpm). The serum was collected in plain tubes and held at (-20C) until it was used.

Evaluation of growth hormone and insulin like growth factor-1 levels

Growth hormone and IGF-1 levels have been estimated by a sandwich chemiluminescence immunoassay (DiaSorin, Italy) [16].

Assessment of metabolic hormones level (thyroid hormones and cortisol hormone)

Minividas device was used to accomplish the thyroid hormones assay (T3, T4 and TSH) and cortisol by using a different kit for each hormone according to the manufactured prescribed process [17].

Lipid profile analysis

Cholesterol, TGs and HDL levels were measured using commercial kits spectrophotometrically [18], LDL and VLDL levels were calculated according to the Friedewald equation [19].

Statistical analysis

The statistical analysis was done using the statistical analysis system (SAS, 2012) program and computer software. All data were expressed as mean ± standard error (SE). Student's t-test was used to compare between the studied groups and Chi-square test was used to significant comparison between the percentages. The level of significance was determined at $P<0.05$ [20].

Results and Discussion

Effect of puberty on the studied parameters in patients with GHD

In this study, patients with GHD (13 year in male and 12 year in female) were classified into two groups according to the age of puberty; the first group included (37) pre-pubertal patients, while the second group included (38) pubertal patients.

Effect of puberty on GH and IGF-1 levels

Effect of puberty on GH and IGF-1 levels in patients with GHD

The data presented in the table (1) shows the effect of puberty on the GH and IGF-1levels.Non-significance (P>0.05) were found in the basal GH levels between the prepubertal group (0.48 ± 0.07 ng/ml) and the pubertal group (0.33 ± 0.05 ng/ml). After 1h stimulation with clonidine, levels of peak GH_2 was significantly (P<0.05) higher in the pubertal group (4.89 ± 0.15 ng/ml) when compared to the pre-pubertal group (3.45 ± 0.87 ng/ml), while after 1.30 h. stimulation with clonidine, levels of the GH_3 showed non-significant (P>0.05) differences between the pre-pubertal group (2.13 ± 0.25 ng/ml) and the pubertal group (2.77 ± 0.37 ng/ml), The levels of IGF-1 were significantly (P<0.01) higher in the pubertal group (166.56 ± 17.03 ng/ml) as compared with the pre-pubertal group (88.62 ± 9.23 ng/ml).

Table (1): Effect of puberty on GH and IGF-1 levels in patients with GHD

Parameters	Mean ± SE		P-value
	Pre-pubertal	Pubertal	
GH1(ng/ml)	0.48^{a} ± 0.07	0.33^{a} ± 0.05	0.0949 NS
Peak GH_2 (ng/ml)	3.45^{b} ± 0.87	4.89^{a} ± 0.15	0.048 *
GH_3 (ng/ml)	2.13^{a} ± 0.25	2.77^{a} ± 0.37	0.1703 NS
IGF-1 (ng/ml)	88.62^{b} ± 9.23	166.56^{a} ± 17.03	0. 002 **
*(P<0.05). ** (P<0.01), NS: Non-Significant.			

- Means with different superscripts within each row are significantly different (P<0.05), (P<0.01)
- Means with similar superscripts within each row are non-significantly different (P>0.05).

The current findings were in agreement with [21] who reported a non-significant difference in the basal GH between the pre-pubertal group and the pubertal group, because of the pulsatile manner of GH secretion, the diagnosis of GHD cannot be done at the basal serum of the studied subjects. Borges *et al*. (2016) [22] suggested that the greatest GH increase occurred after 1h. from clonidine stimulation (GH_2) which is in agreement with this study.

However, in this study the results of the GH_3 after 1.30 h. from clonidine stimulation were statistically less than the GH_2 after 1h. from clonidine stimulation and there were no significant differences between the pre-pubertal and the pubertal groups. This may be due to the pulsate fashion of the GH secretion and it under the feedback regulation of the GHRH and the somatostatin [23]. The current study was also in agreement with other studies [24] which reported that impulsive GH secretion increases during puberty in equivalent with increasing concentrations of sex steroids.

A similar result was also observed by [25] who proposed that the serum IGF-1level in the pre- pubertal group was significantly low when compared to its level in the pubertal group and the serum IGF-1 has proved to be a useful tool in evaluation of the GHD prepubertal children, besides that this recent study were in agreement with previous investigation by [26] who stated that serum IGF-1 level was significantly correlated with sex steroid levels and this correlation showed that increasing sex steroids with pubertal progress increases the IGF-1 level.

Effect of puberty on metabolic hormones level

The data presented in table (2) shows the effect of the puberty on the metabolic hormones level. T3 and T4 levels were significantly (P<0.01) higher in the pre-pubertal group (2.93± 0.07 nmol/L), (113.85

± 4.78 nmol/L), respectively than the pubertal group (1.73± 0.12 nmol/L), (98.19 ± 1.88 nmol/L) respectively. Non-significant (P>0.05) differences were found in levels of TSH between the pubertal group (2.61 ± 0.25 µIU/ml)

and the pre-pubertal group (2.42 ± 0.15 µIU/ml). Also, the results revealed a non-significant (P>0.05) difference in levels of cortisol between the pubertal group (120.12 ± 15.53 ng/mL) and the pre-pubertal group (155.57 ± 23.46 ng/mL).

Table (2): Effect of puberty on metabolic hormones level in patients with GHD

Parameters	Mean ± SE		P-value
	Pre-pubertal	Pubertal	
T3 (nmol/L)	2.93[a] ± 0.07	1.73[b] ± 0.12	0.001 **
T4 (nmol/L)	113.85[a] ± 4.78	98.19[b] ± 1.88	0.001 **
TSH (µIU/ml)	2.42[a] ± 0.15	2.61[a] ± 0.25	0.525 NS
Cortisol (ng/mL)	155.57[a] ± 23.46	120.12[a] ± 15.53	0.209 NS
. ** (P<0.01), NS: Non-Significant.			

- Means with different superscripts within each row are significantly different (P<0.01).
- Means with similar superscripts within each row are non-significantly different (P>0.05).

Similar findings were observed by [27] who reported a significant increase in serum T3 level in the pre-pubertal individuals rather than the pubertal individuals, the reason why children have higher T3 levels at pre-puberty was the higher BMI and adiposity appear to causally increase T3 [27]. On the other hand, in this study the fat mass or the observed changes may represent the changes in the thyroid hormones in preparation for puberty, or be a consequence of changes in other endocrine factors such as GH.

The finding in this study determined a decrease in the serum T4 of the pubertal group as compared to pre-pubertal group that was reported in previous studies [28], the reason why children have higher T4 level was not clear may be due to factors out to the pituitary-thyroid axis such as fat mass and pubertal development [27].

Findings of TSH were in agreement with the previous investigation by [29] which reported a non- significant difference in the serum TSH between the pre-pubertal and the pubertal groups. In the current study, the outcomes of the TSH were determined by the age groups studied and by the definition of the pubertal growth as well as by nutritional or even social considerations. Bülow *et al*. (2005) [30] showed that level of TSH to be affected by multiple variables such as age, gender, ethnicity, adiposity, diet, iodine consumption and geographic region during childhood and adolescence.

Regarding the results of serum cortisol, the same findings were reported by previous researchers

[31] who found no significance difference in serum cortisol between children and adolescence. However, the differences in cortisol levels at particular times of the day and the developmental process of puberty had been stated, which is defined by endocrine and physical changes. Specifically, endocrine changes that including a rise in androgens and gonadotropins and concomitant growth in pubic hair, breast tissue, and external genitalia are initiated and regulated by the same neural and endocrine systems that are responsible for the release of cortisol [32].

Effect of puberty on lipid profile

Effect of puberty on the lipid profile is summarized in table (3). The finding revealed that non- significant differences were found in the cholesterol levels between the pre-pubertal group (171.18 ± 7.64 mg/dL) and the pubertal group (178.78 ± 8.54 mg/dL), while levels of TGs were significantly (P<0.01) higher in the pubertal group (105.50 ± 11.08 mg/dL) than the pre-pubertal group (71.62 ± 3.73 mg/dL). The results showed non-significant (P>0.05) difference in the levels of HDL and LDL between the pre-pubertal group (43.81 ± 2.63 mg/dL) and (99.57 ± 5.68 mg/dL), respectively and the pubertal group (44.23 ± 2.19 mg/dL) and (113.45 ± 7.91 mg/dL), respectively. However, levels of VLDL were significantly (P<0.01) higher in the pubertal group (21.10 ± 2.22

mg/dL) compared to the pre-pubertal group (14.52 ± 0.76 mg/dL).

Table (3): Effect of puberty on lipid profile in patients with GHD

Lipid profile	Mean ± SE		P-value
	Pre-pubertal	Pubertal	
Cholesterol (mg/dL)	171.18[a] ± 7.64	178.78[a] ± 8.54	0.1450 NS
Triglycerides(mg/dL)	71.62[b] ± 3.73	105.50[a] ± 11.08	0.0054 **
HDL (mg/dL)	43.81[a] ± 2.63	44.23[a] ± 2.19	0.901 NS
LDL (mg/dL)	99.57[a] ± 5.68	113.45[a] ± 7.91	0.160 NS
VLDL (mg/dL)	14.52[b] ± 0.76	21.10[a] ± 2.22	0.007 **
** (P<0.01), NS: Non-Significant.			

- Means with different superscripts within each row are significantly different (P<0.01).
- Means with similar superscripts within each row are non-significantly different (P>0.05).

The findings of cholesterol were in agreement with previous investigation by [33] which reported a non-significant difference in serum cholesterol between the pre-pubertal and the pubertal groups, this may be due to the young group in this study includes children and adolescents in different phases of puberty, which may explain why no clear differences were seen in the median cholesterol levels and because cholesterol do not change with age [34].

In the present study, higher TGs level were noticed in the pubertal group as compared to the pre- pubertal group was in agreement with [35] who stated that serum TGs was significantly higher at onset of puberty, beside that plasma lipid levels tended to be different by race, sex or both, TGs levels patterns of change during puberty have differed widely among studies, which may be attributable to differences in study design, population, and method of sexual maturation assessment [36].

Non-significant differences observed in levels of HDL, LDL were in agreement with [34]. This may be due to the lipid profiles of the pre-pubertal girls and boys are very similar but during puberty HDL levels in boys decrease but during puberty HDL levels in boys decrease as a result of testosterone raising while HDL levels in girls do not change [37]. It was reported that LDL levels were similar in boys and girls in pre-puberty and during puberty but after age 20, LDL increased in both boys and girls [38]. The current study included children and adolescents with uneven stages of puberty, which may explain why no clear differences were seen in the median LDL and HDL levels

Present results of VLDL were similar to those that reported by other author [39] who stated that VLDL production increased during puberty due to increasing of TGs level. because VLDL with a TGs content about 50% responsible for carrying fatty acids and TGs from the liver to peripheral tissues [40].

Effect of gender on the studied parameters in patients with GHD Effect of gender on GH and IGF-1 levels

The data presented in table (4) shows the effect of the gender on GH and IGF-1levels. Non- significant (P>0.05) differences were noticed in the basal GH between the boys (0.42 ± 0.06 ng/ml) and the girls (0.38 ± 0.07 ng/ml). Also, non-significant (P>0.05) differences were found in levels of GH_2 (2.83 ± 0.33 ng/ml) and GH_3 (2.16 ± 0.23 ng/ml) in the boys compared with their values in the girls (3.15 ± 0.47ng/ml) and (2.88 ± 0.44ng/ml), respectively. Regarding the levels of serum IGF-1, there were no significant (P>0.05) differences between the boys (126.24 ± 13.06 ng/ml) and the girls (130.91± 18.47 ng/ml).

Table (4): Effect of gender on GH and IGF-1 levels in patients with GHD

Parameters	Mean ± SE		P-value
	Boys	Girls	
Basal GH (ng/ml)	0.42[a] ± 0.06	0.38[a] ± 0.07	0.686 NS
Peak GH2 (ng/ml)	2.83[a] ± 0.33	3.15[a] ± 0.47	0.562 NS
GH3 (ng/ml)	2.16[a] ± 0.23	2.88[a] ± 0.44	0.129 NS
IGF-1 (ng/ml)	126.24[a]± 13.06	130.91[a] ± 18.47	0.832 NS
NS: Non-Significant.			

- Means with similar superscripts within each row are non-significantly different (P>0.05).

The current findings were similar to that of the previous studies [41] which reported a non- significant difference in peak GH between boys and girls. It is well established that the relationship between GH and gonadal steroid levels in children is difficult to estimate since steroid levels are very low before puberty. Although, at puberty, there is a marked increase in GH secretion, which is directly affected by sex steroids because testosterone hormone increased GHRH and somatostatin release from hypothalamus whereas, estrogen increased GHRH but decreased somatostatin release, which in turn established gender-specific GH patterns [42].

In the current study, although the peak GH2 level was higher in the girls than the boys, but statistically the differences were not significant. However, Van Den Berg *et al*. (1996) [43] reported that GH secretion was higher in girls than in boys, both under basal situations and after provocative tests because estrogen appears to motivate GH secretion by decreasing liver secretion of IGF-1 resulting in stimulation of the pituitary to secrete GH [43]. Also, the current results of GH3 were similar to [21] who reported a non-significant difference after (1h.and 1.30 h.) clonidine stimulation due to the pulsating manner of the GH secretion.

Regarding to the findings of IGF-1 in this study, despite the IGF-1 level was higher in the girls than the boys, but statistically the differences was insignificant, the explanation behind that was the selected cases of boys and girls were pre-pubertal and pubertal. Juul *et al*. (1994) [45] suggested that IGF-1 levels increased gradually in early childhood, with a sudden increase during puberty, current studies found that the estrogen receptors motivate many singling pathways and kinase enzymes which in turn rapidly induces phosphorylation of the IGF-1 receptors and increases IGF-1 expression, girls had greatest IGF-1 levels at the mean age of 14.5 year. and boys at 15.5 year. This difference between the sexes is in harmony with the different growth form between boys and girls [46].

Effect of gender on metabolic hormones level

Effect of gender on metabolic hormones level is shown in table (3-11). The findings revealed that non-significant (P>0.05) differences were found in the T3 and the T4 levels between the boys (2.45 ± 0.08 nmol/L) and (96.49 ± 2.19 nmol/L), respectively and the girls (2.30 ± 0.13 nmol/L) and (100.75± 2.94 nmol/L), respectively. Also, non-significant (P>0.05) differences were noticed in levels of TSH and cortisol between the boys (2.50 ± 0.17 µIU/ml) and (137.49 ± 17.95 ng/mL), respectively and the girls (2.54 ± 0.27 µIU/ml) and (137.78 ± 22.93 ng/mL), respectively.

Table (5) Effect of gender on metabolic hormones level in patients with GHD

Metabolic Hormones	Mean ± SE		P-value
	Boys	Girls	

T3 (nmol/L)	2.45^{a} ± 0.08	2.30^{a} ± 0.13	0.315 NS
T4 (nmol/L)	96.49^{a} ± 2.19	100.75^{a}± 2.94	0.240 NS
TSH (µIU/ml)	2.50^{a} ± 0.17	2.54^{a} ± 0.27	0.896 NS
Cortisol(ng/mL)	137.49^{a} ± 17.95	137.78^{a} ± 22.93	0.992 NS
NS: Non-Significant.			

• Means with similar superscripts within each row are non-significantly different (p>0.05).

Similar results were also observed by [47] who reported no sex differences during the childhood and adolescence in the studied cases pubertal. It was stated that the development did not affect the concentration of thyroid hormones and TSH in children. This may be due to sex steroids might have a parallel modulation effect through puberty in both genders, adequate iodine intake, the chronological age, weight and height were almost identical between both genders [48]. However, the reference values of adults are not abdicable to children and teens because thyroid volume affected by puberty specially menarche in girls, so the thyroid hormone levels may change and be sex-age depend patterns [49].

In the current study, all the studied subjects from boys and girls were euthyroid because the monitoring of thyroid profile is an essential pre-step before the diagnosis of GHD, all pediatric endocrinologists have been recommended to monitor thyroid function before and during rhGH therapy mostly in the first year of therapy when the largest decrease in FT4 happens [50].

The current finding of cortisol level was similar to the previous study [51] who reported no gender differences between boys and girls. The explanations behind that is the cortisol levels did not correlate with the dose of clonidine used and there was no correlation between the peak level of GH and the reduced cortisol levels. A similar result done by [52] found no gender differences in cortisol. However, there were no gender differences between the two groups in this study because the selected samples were limited or due to various factors, such as age, fast duration and puberty. In addition, all the selected samples were obtained in the morning (8-11 a.m.) which impact the levels of cortisol.

Effect of gender on lipid profile

The data presented in table (6) shows the effect of gender on the lipid profile. Non-significant differences (P>0.05) were noticed in levels of cholesterol and TGs between boys (170.13 ± 7.67 mg/dL) and (83.69 ± 5.88 mg/dL), respectively and girls (165.13 ± 7.82 mg/dL) and (96.43 ± 12.74 mg/dL), respectively. Also, non-significant differences (P>0.05) were noticed in levels of HDL, LDL and VLDL between boys (42.64 ± 2.35 mg/dL), (110.75 ± 6.63 mg/dL) and (16.73 ± 1.17 mg/dL), respectively and girls (46.10 ± 2.34 mg/dL) (100.38 ± 7.22 mg/dL) and (19.53 ± 2.54 mg/dL) respectively.

Table (6) Effect of gender on lipid profile in patients with GHD

Lipid profile	Mean ± SE		P-value
	Boys	Girls	
Cholesterol (mg/dL)	170.13^{a} ± 7.67	165.13^{a} ± 7.82	0.661 NS
Triglycerides(mg/dL)	83.69^{a} ± 5.88	96.43^{a} ± 12.74	0.316 NS
HDL (mg/dL)	42.64^{a} ± 2.35	46.10^{a} ± 2.34	0.321 NS
LDL (mg/dL)	110.75^{a} ± 6.63	100.38^{a} ± 7.22	0.305 NS
VLDL (mg/dL)	16.73^{a} ± 1.17	19.53^{a} ± 2.54	0.271 NS
NS: Non-Significant.			

• Means with similar superscripts within each row are non-significantly different (P>0.05).

Similar results were reported by other authors [53] who stated that sex did not show any association with the different types of lipid profile among boys and girls. The explanation behind these results is that male and female cases were within the same rank of age ranging from childhood to adulthood, beside that lipid profile variations tends to be associated with overweight and obese individual more than normal weight individual [54]. In the current study, the most studied cases were within the underweight and normal weight categories, therefore the biochemical lipids tests showed related results between boys and girls.

Conclusions

It can be concluded from the recent study that the impact of puberty on certain parameters such as GH2, IGF-1, TGs and VLDL were higher in pubertal patients with GHD than in pre-pubertal patients with GHD, T3 and T4 levels were higher in pre-pubertal patients with GHD compared to their levels in pubertal patients with GHD. The observed changes may represent the changes in the thyroid hormones in preparation for puberty. The gender, on the other hand, had no effect among all the studied parameters.

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