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FULL PAPER

The influence of growth hormone on some interleukins levels in patients with growth hormone deficiency

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The aim of this study is to evaluate the influence of growth hormone on some interleukins levels in patients with growth hormone deficiency by measuring and correlating many biochemical markers. Blood samples were gathered from study participants to estimate levels of basal growth hormone, growth hormone after 60 min (GH_2) and 90 min (GH_3) induction with clonidine, respectively, Insulin-like growth factor, interleukin-4, interleukin-6, and resistin. The outcomes of the anthropometric measurements of the studied groups exposed a significant ($p < 0,05$) differences in mean of BMI and BMI Z score between the GHD and non-GHD. The outcomes presented significant ($P < 0.05$) decrease in levels of basal GH, GH_2, GH_3, and IGF-1 in the GHD compared to the non-GHD. The outcomes presented a significant ($p<0.05$) fall in level of IL-4, IL-6 and resistin in the GHD compared to the non-GHD. The breakdown of the study groups revealed that males made up (53.3%) of the GHD, while females made up (46.7%), whereas the non-GHD (64.4% males and 35.6% females). The percentage of underweight in the GHD (71.1%) was lower than in the non-GHD (80%), whereas the percentage of normal weight was greater in the non-growth hormone deficiency (20%) compared to the GHD (17.8%). The distribution of the studied groups by gender displayed that non-significant ($p>0.05$) variances were seen in basal GH level, GH_2, GH_3 between males and females, IGF-1 was significant ($p<0.05$) decreases in males compared with females.

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Introduction

Growth hormone is a polypeptide hormone with a half-life of 20-30 min that is secreted via the anterior pituitary somatotropin cells. GHRH and somatostatin, respectively, increase and inhibit GH secretion [1].

Growth hormone deficiency is an endocrine disease that impacts a person's life from birth to teenage years and beyond due to GH excretion difficulties or other causes. Growth hormone deficiency, because of hypopituitarism, may occur in childhood or adulthood. Childhood-onset disease is commonly genetic or idiopathic, while in adults, the hypopituitarism is produced mainly via causes such as a pituitary surgery,

inflammation, irradiation, apoplexy and pituitary tumor [2].

Insulin like growth factor-1 is a polypeptide hormone with only one chain. It is created in response to GH stimulation in the liver and local tissue, but it is liver IGF-1 that has the most impact on the pituitary gland [3].

Interleukin-4 is cytokine produced largely by mast cells, Th2 cells, eosinophil, and basophils that acts as a strong immune regulator. IL-4 is a cytokine that influences immunological responses in a variety of ways [4].

Interleukin-6 is a cytokine having many biological functions .The adipose tissue secreted about 15-30% of the circulating IL-6. It affects the immune system in a variety of ways, and because of its hormone-like properties, it can affect the homeostatic process. Because it has both anti-inflammatory and pro-inflammatory effects, it is commonly employed in clinical intervention [5].

Human resistin is a 12.5 kDa cysteine-rich peptide comprising 108 amino acids in its mature form. The human resistin gene is found on chromosome 19. The genes have significantly different developer areas suggesting different tools of regulation tissue dissemination and purposes. Because the advanced protein tends to form oligomers, it can be found in human serum in a variety of small and tall molecular weight practices [6].

Studied subjects

The current study contains a total (90) subjects. Forty-five GHD (23 boys and 27 girls) and forty-five (18 boys and 27 girls) non-GHD were employed as a control group. The participants' ages ranged from (3-16 year). Questionnaires were used to record the anthropometric measurements of the subjects.

Collection of blood samples

After an overnight fast, the study participants' venous blood samples of 5 mL were obtained. The blood was inserted in a fresh gel tube and permitted to coagulate for 30 min at $37c^0$. By centrifuging the tubes at 3000 rpm for five min, the serum was recovered and kept at -$20C^0$ until needed.

BMI, BMI percentile and BMI Z-score evaluation

The following equation was used to calculate the BMI of the subjects investigated [7].

BMI (kg/m^2)= Weight (kilograms)/Height ($meters^2$)

Percentiles are used to rank a person's position by stating what percentage of the sample group he or she would surpass. A Z-score is calculated by dividing the difference between an individual's value and the mean value of the sample group by the standard deviation of the sample group [8].

Results and discussion

The study participants were separated into groups depending on their BMI.

The outcomes (Table 1) displayed that the percentage of the underweight was 71.1% in GHD compared to non-growth hormone deficient (80%), while the percentage of normal weight was 17.8 % in GHD compared to non-growth hormone deficient (20%). Non-significant difference was noticed in overweight and obese.

TABLE 1 The study participants were separated into groups depending on their BMI.

Groups / Parameters		Growth Hormone Deficiency (GHD) No.	%	Non-growth hormone deficiency No.	%
BMI (Kg/m²)	Under weight (<18.5)	32	71.1	36	80
	Normal weight (18.5-24.9)	8	17.8	9	20
	Over weight (25-29.9)	4	8.9	-----	-----
	Obese (>35)	1	2.2	-----	-----
Chi-Square (X^2)		0.151			
No Significant difference by using Chi-Square Test at 0.05 level.					

The same answers were reported by other researcher [9] who revealed that the most of GHD were underweight. These findings could be due to a variety of factors, including socioeconomic level, hunger, and way of living. The non-growth hormone deficiency had a higher prevalence of normal weight than the GHD patients, which can be explained by the fact that the non-GHD average length and growth are normal, Furthermore BMI cannot be used in the diagnostic techniques of GHD. The present answers are in a good agreement with [10] who displayed that growth hormone production is reduced in obese people, and both natural and induced peak GH levels are decreased in obese and overweight people with GHD. Obesity causes a decrease in GH secretion, which is paralleled by the increased insulin resistance and other metabolic syndrome [11].

Anthropometric measurement of growth hormone deficiency and non-growth hormone deficiency

Table 2 shows the anthropometric measurements of growth hormone deficiency and non-growth hormone deficiency. Non-significant ($p>0.05$) variances were observed in age (11.26± 3.30 year) and weight (30.28± 13.98 kg) and height (127.28± 16.74 cm) of the growth hormone deficiency compared with non- growth hormone deficiency (11.26± 3.32 year) and (26.48± 7.20 kg) and height (127.66± 13.24 cm), respectively.

TABLE 2 Anthropometric measurement of growth hormone deficiency and non- growth hormone deficiency

Groups / Parameters	Growth Hormone Deficiency (GHD) No. (45)	Non-growth hormone deficiency No. (45)	P-value
Age (year)	11.26 ± 3.30	11.26 ± 3.32	1.00
Weight (kg)	30.28 ± 13.98	26.48 ± 7.20	0.10
Height (cm)	127.28 ± 16.74	127.66 ± 13.24	0.90
BMI (kg/m²)	18.05 ± 5.82	16.01 ± 2.57	*0.03
BMI percentile (%)	10.34 ± 5.92	8.64 ± 4.98	0.14
BMI Z-score	0.22 ± 1.26	-0.22 ± 0.55	*0.03
-The data was given as Mean ± SD			
*Significant difference between two independent means using Students-t-test at 0.05 level.			

A non-significant variance in the mean of age among the growth hormone deficiency and non-growth hormone deficiency could be due to the two group's subjects having similar age ranges.

The latest discoveries of the weight are identical to that of a previous research [12]. There was no statistically significant difference in weight between growth hormone deficiency and non-growth hormone deficiency, according to the study. Yet, the current findings contradict those reported by some other group [13]. The disparities between the researches could be attributed to changes in sample size, nutritional status, and study subjects' lifestyles. Similar to the present finding, a preceding study [14] growth hormone deficiency and non-growth hormone deficiency did not differ in height significantly. The idea of GHD is one of the reasons of short height and has an impact on bone maturation that could explain this conclusion. Also, regular exercise, food habits, and standard of living all influence kid's height [15].

In terms of the current state of BMI, Results contradict the conclusions of another research [16] which described non-significant difference in BMI among the growth hormone deficiency and non-growth hormone deficiency, while they are in agreement with other reports [17]. This outcome might be related to the fact that the BMI calculation takes into account both weight and height [18]. The current BMI percentile % findings are comparable with that of previous research [19]; according to the study, there were no significant differences in BMI % between growth hormone deficiency and non-growth hormone deficiency Because a person's BMI percentile is linked to their health risk, most notably, the BMI percentile number for overweight and underweight children of all ages are the same [20]. The current BMI Z-score values are consistent with previous research [21]. According to the research, growth hormone deficiency and non-growth hormone deficiency had significant differences in BMI Z-score. BMI Z-score corresponds to percentiles on growth charts and can be converted to BMI-for-age percentiles using a normal distribution table, however this is not required for clinical application [22].

Levels of growth hormone and IGF-1 in GHD and non-growth hormone deficiency

The outcomes shown in Table 3 established that the levels of basal GH had significant ($p<0.05$) decrease in GHD (0.46± 0.65 ng/mL) than those of non-growth hormone deficiency (1.15± 1.54 ng/mL). The levels of growth hormone after 60 minutes provocation with clonidine (GH_2) (3.30± 2.04 ng/mL) and after 90 minutes provocation with clonidine (GH_3) (1.85± 1.51 ng/mL) in the GHD showed highly significant ($p<0.05$) decrease than their value in non-growth hormone deficiency (13.24±5.05 ng/mL) and (8.16 ± 6.42 ng/mL), respectively.

The greatest value of GH (peak) was taped after 60 minutes provocation with clonidine (GH_2) in two examined categories, according to the outcomes.

When assessing the levels of insulin growth factors-1in two categories that were investigated, the outcomes exposed that levels of IGF-1 had significant ($p<0.05$) decrease in the GHD (181.71 ± 122.02 ng/mL) than in non-growth hormone deficiency (217.4±108.09 ng/ mL).

TABLE 3 Levels of GH and IGF-1 in growth hormone deficiency and non-growth hormone deficiency

Groups / Parameters	Growth Hormone Deficiency (GHD) No. (45)	Non-growth hormone deficiency No. (45)	P-value
Basal GH (ng/mL)	0.46 ± 0.65	1.15 ± 1.54	*0.004
GH_2 (ng/mL)	3.30 ± 2.04	13.24 ± 5.04	*0.0001
GH_3 (ng/mL)	1.85 ± 1.51	8.16 ± 6.42	*0.0001
IGF-1 (ng/mL)	181.71 ± 122.02	217.4 ± 108.09	*0.001

-Data were presented as Mean ± SD

*Significant difference between two independent means using Students-t-test at 0.05 level.

An earlier study came up with the same results [23]. Another study, on the other hand, reported no significant variance in basal GH among GH deficiency and non-growth hormone deficiency [24]. This is owing to the pulsatile nature of GH secretion, which is little during the day and increases throughout sleep, as well as stress and other factors, and thus it is unreliable in diagnosis [25]. The current GH_2 and GH_3 values are consistent with those seen in prior study [26]. When comparing the GH deficiency patients to the non-growth hormone deficiency on the one hand, and their levels after 60 min and after 90 min on the other, the identical results were found. This could be due to the fact that GH secretion is pulsatile, raising in response to a provocation test [27].

The outcomes of IGF-1 levels, on the other hand, are consistent with those of another study [28] that found a substantial reduction in IGF-1 levels in GHD as compared to non-growth hormone deficient. This may be because IGF-1 is a reliable predictor of GH activity [29].

Levels of interleukin-4, interleukin-6 and resistin in growth hormone deficiency and non-growth hormone deficiency

Table 4 shows levels of IL-4, IL-6 and resistin of growth hormone deficiency and non-growth hormone deficiency.

The outcomes exposed that levels of IL-4 were significant ($p<0.05$) increasing in GHD (248.53± 75.01ng/mL) compared with non-growth hormone deficiency (174.14±59.22 ng/mL), while levels of IL-6 were significant ($p<0.05$) increasing in GHD (117.04±38.66 ng/mL) compared with non-growth hormone deficiency (28.33 ±22.62 ng/mL).

Levels of resistin had significant ($P<0.05$) increase in GHD (6.29±3.31 ng/mL) compared with non-growth hormone deficiency (1.92 ±1.52 ng/mL).

TABLE 4 Levels of interleukin-4, interleukin-6 and resistin in growth hormone deficiency and non-growth hormone deficiency

Groups / Parameters	Growth Hormone Deficiency (GHD) No. (45)	Non-growth hormone deficiency No. (45)	P-value
IL-4 (ng/mL)	248.53 ± 75.01	174.14 ± 59.22	*0.0001
IL-6 (ng/mL)	117.04 ± 38.66	28.33 ± 22.68	*0.0001
Resisen (ng/mL)	6.29 ± 3.31	1.29 ± 1.52	*0.0001

- The data was given as Mean ± SD

*Significant difference between two independent means using Students-t-test at 0.05 level.

The results of IL-4 and IL-6 disagree with a previous study [30] observing that IL-4 and IL-6 levels are greater in GHD than non-growth hormone deficiency. Perhaps the creation of IL-6 and IL-4 may be stimulated by growth hormone. Short-term growth hormone can

affect cytokine release in healthy youngsters demonstrating that growth hormone has a direct impact on the immune system [31].

The present results of resistin,–were in agreement with a previous study [32] indicating that the two categories had considerable disparities.

Resistin is found at very low amounts if at all in human adipose cells, but at very high levels in macrophages, and bone marrow cells, implying that it is largely produced in the stomovascular parts of adipose tissue, which are common in obese people [33].

Impact of the gender on the levels of growth hormone and insulin growth factor-1

Table 5, the influence of gender on GH and IGF-1 levels is shown. Non-significant ($p>0.05$) variances were observed in basal GH level among males (0.66± 0.80 ng/mL) and females (0.77± 0.92 ng/mL). Non-significant ($p>0.05$) differences in levels of GH_2 and GH_3 (8.38± 6.74 ng/mL), (5.05± 5.97 ng/mL), respectively in boys compared with their levels (8.14± 5.78 ng/mL), (4.96± 5.24 ng/mL), respectively in girls.

IGF-1 levels, the present study shows they were significant ($p<0.05$) decreases in males (187.36± 119.38ng/mL) compared with the females (214.12± 111.59 ng/mL).

TABLE 5 Effect of gender on GH and IGF-1 levels

Groups / Parameters	Male	Female	P-value
Basal GH (ng/mL)	0.66 ± 0.80	0.77 ± 0.92	0.55
GH_2 (ng/mL)	8.38 ± 6.74	8.14 ± 5.78	0.86
GH_3 (ng/mL)	5.05 ± 5.97	4.96 ± 5.24	0.94
IGF-1 (ng/mL)	187.36 ± 119.38	214.12 ± 111.56	*0.037

- The data was given as Mean ± SD

*Significant difference between two independent means using Students-t-test at 0.05 level.

The present results of basal GH level and their levels after stimulation (GH_2 and GH_3) are similar to those that stated by previous researchers such as [34].who indicated that no significant differences were found between girls and boys. Gender has a varying effect on stimulated GH secretion depending on the response type due to the complex links among sex steroids and sensor neuroendocrine systems that govern GH secretion Women have a higher pulse frequency and basal levels daytime, but men's GH production is largely nocturnal, with daytime quiescence [35].

In the current study, although the GH_2 level was higher in boys than girls, but statistically the changes were not significant. However, the current findings are in disagreement with other study [36]. For men, the link between gonadal and GH status appears to be robust whereas for woman, it appears to be less so [37].

The current outcomes of GH_3 was similar to [38] which reported non-significant differences after clonidine stimulation due the pulsating manner of the growth hormone excretion.

IGF-1 levels can be shown by other authors [39] reported that IGF-1 levels were greater in the girls than in boys. Estrogens suppress hepatic IGF-1 production, removing the negative feedback loop and resulting in higher GH levels. Also, IGF-1 levels starts out modest at birth progressively grow throughout childhood, peak soon before puberty, reach adult levels and then start to fall with age [40].

Distribution of the studied subjects according to gender

According to gender of studied groups. it can be seen from the data in table 6, found the

majority of the GHD (53%) were boys while (46.7%) were girls, that is statistically significant (p<005). While (64.4%) were boys, (35.6 %) were girls which are statistically considered as significant (P<0.05).

TABLE 6 Distribution of the studied subjects according to gender

Groups / Gender	Growth Hormone Deficiency (GHD)		Non-growth hormone deficiency Control		P-value
	No.	%	No.	%	
Male	24	53.3	29	64.4	*0.0001
Female	21	46.7	16	35.6	*0.0001

*Significant difference between two independent means by using Students-t-test at 0.05 level.

A similar outcomes has also been observed by [41].Males are referred to endocrine clinics for growth problems in greater numbers than females, and pituitary issues account for the majority of GHD cases in men. Males may be more vulnerable than females to pituitary function and specific GH secretion [42].

Conclusion

The current study concludes that the GH basal serum cannot be used to diagnose GHD. Insulin like growth factor-1 is a good predictor of growth hormone activity. Growth hormone deficiency seems more prevalent in males. The pulsatile nature of growth secretion resulted in an increase after 60 minutes of clonidine provocation compared to 90 minutes of clonidine provocation. Levels of IL-4, IL-6, and resistin are affected by GHD.

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