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Correlation of Insulin Like Growth Factor-1 and Insulin-Like Growth Factor Binding Protein with LH, FSH and Testosterone in Iraqi Children with Growth Hormone Deficiency

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Abstract

Insulin like growth factor-1 has metabolic and growth-related roles all over the body and is strongly associated and regulated by growth hormone. It is produced by almost any type of tissue, especially the liver. The study aimed to measure insulin like growth factor in growth hormone deficient patients and find its relation with other studied parameters. The Subjects in the study were 180 studied in the National Diabetic Center for Treatment and Research/Al-Mustansiriya University in Baghdad/Iraq for the period from November 2021 to April 2022. Blood was drawn and investigated for the levels of IGF-1, IGFBP-3, LH, and FSH. Also testosterone and statistical analysis was carried out to find the potential correlations. The results relived that the gender was not affect the levels of either parameter, IGF-1 was found to be positively correlated with age, BMI, and IGFBP-3. While IGFBP-3 was found to be positively correlated with the levels of IGF-1, LH, FSH and testosterone. From the results of the current study, it can be concluded that the levels of GH as well as the levels of IGF-1 and IGFBP-3, have significant difference between the NGHD and the patients' group.

Keywords: Insulin like Growth Factor-1, Insulin-like Growth Factor Binding Protein.

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1- Introduction

Growth factor similar to insulin I (IGF-I) is a crucial growth and differentiation factor that is produced in a variety of tissues, particularly the liver, and it is closely related to the growth hormone the pituitary produces [1]. 90% of the circulating hormone is bound by IGFBP-3, which binds IGF-1 specifically and lengthens its half-life [2].

Additionally, insulin-like growth factor 1 exerts strong metabolic, insulin-like effects on lipid and carbohydrate metabolism. IGF-I probably has a significant impact on how well the central nervous system works as well [3]. IGF-1 is a powerful neurotrophic and neuroprotective factor that promotes the proliferation, survival, and growth of neurons in the brain. A wide range of functions, including proliferative, mitochondrial protection, cell survival, tissue growth and development, anti-inflammatory and antioxidant, antifibrogenic, and antiaging, have recently been linked to IGF-I [4 - 6]. IGF-I is thought to be crucial for skeletal development and serves as a sign of the patient's nutritional condition because it declines during hunger [7].

Aging and decreasing circulating levels of IGF-1 are associated with a number of illnesses, including cardiovascular disease, metabolic syndrome, and neurological disorders [8]. A set of soluble, high-affinity IGF-binding proteins (IGFBPs) tightly govern how IGFs interact with IGF receptors to prevent the unintended effects of IGFs, such as hypoglycemia and unchecked cellular growth. One of three processes—binding of IGFBPs to molecules in the extracellular matrix, phosphorylation of IGFBPs, or proteolytic destruction of IGFBPs—leads to its release from its binding proteins [9]. In addition to the hepatocytes, the kidney, stomach, uterus, and placenta all manufacture IGFBP-3 through the sinusoid epithelial cells of the liver. Age, nutrition, and GH all affect how much of it is produced [10].

It is in charge of a variety of bodily functions, but those that are related to IGF regulation include the movement of IGFs in plasma, the management and control of their clearance from the vascular space, the targeting of IGFs for specific tissues, and the modification of their interactions with their receptors [11]. IGFBP-3 is believed to be associated with the retinoid acid X receptor alpha and hence affect gene expression in an IGF independent manner [12]. Steroid hormones that interact with vertebrate steroid hormone receptors are known as sex hormones. Androgens, estrogens, and progestogens are the sex hormones. Male secondary sexual traits are caused by androgens, which are produced in the testicles, ovaries,

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and adrenal glands during puberty in both males and females [13]. Androgens are also present in females, yet in less amounts. They play a role in desire and sexual excitement, and they also prevent early uterine contraction in pregnant women by relaxing the myometrium's muscles. And in both men and women, they serve as the building blocks for estrogens [14].

Estrogen plays a variety of impacts on metabolism, behavior, cardiovascular health, and bone density, all of which have an impact on reproduction in both males and females [15]. However, nongonad organs such the liver, heart, skin, and brain can also create a negligible but considerable amount of estrogens. Estrogen is principally produced in the ovaries, corpus luteum, and placenta [16]. Regarding the reproductive system, estrogen induces the thickening of the vaginal wall and the maintenance of vasculature and skin. It also stimulates uterine and endometrial growth and vaginal lubrication. The midcycle ovulation is brought on by an increase in luteinizing hormone, which is stimulated by an increase in estrogen [17]. Another sex hormone that is primarily found in females is progesterone. Progesterone can be produced by the gonads or the adrenal glands, and the progesterone produced by the ovaries is primarily transported in the blood to carry out its biological function, whereas progesterone produced by the adrenal glands is largely converted into glucocorticoids and androgens, allowing the endometrium to transition from a proliferative to a secretory stage. Progesterone also appears to have an inhibitory effect on female [18].

The gonadotropins are peptide hormones that control the activity of the ovary and the testicles and are crucial for healthy development, sexual development, and reproduction. Follicle-stimulating hormone (FSH) and luteinizing hormone are two of the human gonadotropins produced by the pituitary (LH) [19]. The hypothalamus, the pituitary, and the gonads are all components of the neurological pathway that luteinizing hormone is a part of. Pulsatile GnRH production from the hypothalamus triggers the release of LH. Numerous neurotransmitters, including dopamine, serotonin, norepinephrine, glutamate, opiate, and galanin, regulate GnRH in its own body. Kisspeptin is an essential GnRH regulator, LH generally aids in the maturation of progenitor cells. LH stimulates the production of testosterone in the testes' Leydig cells in men, LH causes the ovaries to produce steroid hormones in females [20].

The regulation of testosterone synthesis in male fetuses shifts from hCG-influenced to LH-driven about weeks 15 to 20 of gestation. As with LH, the production of follicle stimulating hormone is negatively influenced by estrogen levels in females. The most important factor in determining the size of the testicles in young boys is Sertoli cell growth, which is stimulated by FSH in males. By encouraging granulosa cells in the ovarian follicles to create aromatase, which transforms androgens produced by the thecal cells into estradiol, FSH is responsible for estrogen synthesis in females. When the menstrual cycle is in the follicular phase, it is also in charge of follicular development [20].

2- Materials and Methods

2.1. Patients' selection

This Cross-sectional study was carried out in the National Diabetic Center for Treatment and Research/Al-Mustansiriya University in Baghdad/Iraq for the period from November 2021 to April 2022, after ethical consent obtained from the review board and a verbal consent of participation from the subjects, the study included 180 subjects that suffer from short stature were divided according to their GH level into the groups: 100 patients suffering from growth hormone deficiency (patients' group) 80 of disease-free subjects (non-growth hormone deficient group).

The Inclusion criteria: short statured children aged 3-18 years old, and Exclusion criteria this study excluded elderly participants, kids with diabetes, liver or kidney problems, and kids on cortisone, thyroxin, or estrogen drugs.

2.2. Collection of samples and measurement of parameters

Based on the patient's medical history, physical and clinical examination, and GH-IGF-1 axis biochemical tests, the diagnosis of GHD was made. The research's parameters will be IGF-1, IGFBP-3, FSH, LH, and testosterone. Five milliliters of blood were drawn, and it was centrifuged for ten minutes at 3000 rpm. Age was taken and body mass index of the studied subjects was measured by the following equation: BMI=(body weight)/(hight^2) then it was categorized to underweight (<5th percentile), normal (5th-85th percentile), and overweight (>85th percentile).

One-step sandwich chemiluminescence immunoassay was used to assess the presence of insulin-like growth factor. After a series of reactions, isoluminol conjugate was formed, which could then be detected using a photomultiplier such as RLU [21]. Using the quantitative sandwich immunoassay method, the amount of insulin-like growth factor binding protein is determined, concentration of follicular stimulating hormone and luteinizing hormone. The hormone testosterone was measured using the competitive binding approach, which produces a yellow product that corresponds to the hormone's concentration as determined by the standard curve [22, 23].

2.3. Statistical analysis

Statistical analysis was done using SPSS 23 using the means and standard deviation, t-test, chi square, correlation and analysis of variances, accordingly. P value was considered significant if less than 0.005.

3- Results and Discussion

In this study, 76 male participants were studied, 44 of which were GH deficient while the remaining were of the

non-growth hormone deficient group (NGHD), 56 females participants had the disease and another 48 were of the NGHD group (disease free), the distribution of studied groups according to gender showed no significance correlation using the chi square test at the significance level of 0.05 (Table 1).

Table 1. Groups Distribution According to Age and BMI

Parameter	Groups	Growth Hormone Deficiency (GHD)		Non-growth hormone deficient (NGHD)	
Gender		Number	Percentage	Number	Percentage
	Male	44	44%	32	40%
	Female	56	56%	48	60%
BMI	Underweight	81	81%	72	90%
	Normal Weight	15	15%	8	10%
	Overweight	4	4%	-	-
	Obese	-	-	-	-

No Significant difference using Chi-Square Test at 0.05 level.

These results were found to be in accordance to those by Claessen et al., 2013 [24]. However, studies by [25, 26] Found a prominent male predominance in patients being treated for this disease, probably because of the increased search for diagnosis of short stature among males than those among females.

The table also shows the distribution of groups according to BMI that was also found to be non-significant. The same results were reported by other researcher [27]. 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. Gender was not found to be significantly affecting the level of IGF-1 or IGFBP-3, as shown in (Table 2).

Table 2. Effect of Gender on Levels of IGF-1 and IGFBP-3

Parameter	Mean ± Std		p-value
	Male	Female	
IGF_1	132.275±13.757	121.542±10.224	0.52
IGFBP_3	9.7388±0.36249	8.8772±0.30377	0.07

Higher level of IGF-1 was found in females in a study done by [28]. which opposes our study. No difference in IGFBP-3 between males and females, as in our study, in the study done by Esberg et al,.2004 [29]. Direct factors like protein-calorie intake, catabolic stressors, thyroxine, insulin, binding affinity of the acid-labile subunit for IGF-I/IGFBP-3, zinc, parathyroid hormone, parathyroid hormone-related peptide, and platelet-derived growth factor can all have an impact on the level of circulating IGF-I. IGF-I levels in youngsters are similar in prepubescent boys and girls [30]. Even after Tanner stage correction, IGF-I levels vary during puberty [30]. These differences are thought to be primarily impacted by GH state, which may then be influenced by sex hormones. This theory has been supported by evidence showing that healthy young females' IGF-I levels alter over the menstrual cycle. Additionally, it has been demonstrated that blood IGF-I levels in healthy midlife adults are only moderately predicted by GH status [31], and the finding that some hypopituitary people with overt GHD have normal IGF-I levels strongly suggests that circulating IGF-I also depends on factors unrelated to GH.

In Table 3, shows the effect of gender on LH, FSH, and testosterone, and it was found that there were no significant differences between the first two with p values of (0.01, 0.5), respectively. While testosterone showed a significant difference between males and females with p value being 0.02. In accordance with our study, both of LH and FSH were found to not be significantly different between males and females in a study conducted by Roper et al., 2015 [32].

Table 3. Effect of Gender on LH, FSH, and Testosterone

Parameter	Mean ± Std		p-value
	Males	females	
LH	39.2437±0.28405	38.0108±0.36053	0.01
FSH	9.2925±0.21986	9.0557±0.35329	0.5
Testosterone	1.1238±0.02470	1.0310±0.03046	0.02

Testosterone, as it is the main sex hormone in males, was hence found to be higher in males than in females, in our study and in others done by Durdiakova et al., 2011 [33]. Puberty is a complex process that helps children mature, develop secondary sexual traits, and learn how to reproduce. Normal pubertal transition is triggered by central processes, with increased GnRH and gonadotropin production driving the gonadal function. Furthermore, it appears that a sufficient energy supply and nutritional balance are necessary for the central beginning of the pubertal shift. At the testicular level, GH stimulates gametogenesis and the generation of steroid hormones during puberty and the reproductively mature phase, as well as the growth and development of the gonad during infancy and adolescence. With increasing age, the rate of GH synthesis doubles, reaches a maximal peak during pubertal maturation, and thereafter declines [34].

The IGF-1 released in response to circulating GH levels also supports this mechanism. Studies that have revealed how testicular volume changes when patients with childhood-onset growth hormone deficit (CO-GHD) are treated with replacement dosages of GH [2], provide evidence to support this. Additionally, GH encourages the growth and differentiation of internal testicular anatomy, including seminiferous tubules (ST). In Table 4 showing the correlations between IGFBP-3 and IGF-1, LH, FSH and testosterone were positive in the patients group.

Table 4. Association of IGF-1 and IGFBP-3 with Studied Parameters

Parameter	IGF-1		IGFBP-3	
	r	p	r	p
Age	0.498**	0.000	.088	.382
BMI	0.229*	0.022	-.052	.608
IGF-1	-	-	.277**	.005
IGFBP_3	0.277**	0.005	-	-
LH	0.036	0.724	.353**	.000
FSH	0.075	0.461	.508**	.000
Testosterone	0.147	0.145	.349**	.000

In our study, age was found to be negatively correlated with the level of IGF-1 this agreement with a study by Gubbi et al., 2018 [35]. Which is probably because of increased age range included in their study. In accordance with our study, BMI was found to be positively associated with IGF-1 level in the study of Lewitt et al., 2014 [36]. Two other studies showed the positive correlation between IGFBP3 with IGF-1 [37, 38]. Luteinizing hormone was also found to be in a positive association with the level of IGFBP-3 by Adam et al., 2000 [39]. On the other hand, FSH showed a negative correlation with IGFBP-3 by Adachi et al., 1995 [40], and testosterone was suggested to have a positive correlation in the study of Gross et al., 2004 [41]. Since plasma IGF-1 concentration has been reported to decrease with age, this suggests that there is a decline in protein synthesis capacity in many tissues with aging, including the liver, skeletal muscle, brain, and bone. This decline is closely associated with changes in IGF-1 and may be caused by changes in IGF-1 secretion, IGF-1 mRNA levels, or changes in the regulation of IGF-1 binding proteins. The age range of the samples in our study could be the cause of the opposite outcome in this area. The biological consequences of mild dietary restriction prevent the age-related decline in protein synthesis and subsequent IGF-1 depletion while still delivering vital nutrients. Hyperinsulinemia due to obesity reduce IGF1 binding protein and subsequently increase IGF1 free concentrations. Thus, obesity may highly dysregulate IGF1 system despite the reduction of growth hormone [42].

Obesity-related hyperinsulinemia decreases IGF1 binding protein and hence raises IGF1 free concentrations. Thus, despite the decrease in growth hormone, obesity may have a significant dysregulation of the IGF1 pathway [42]. Without a pathogenic cause, the concentration of IGF-1 is highly correlated with the levels of its binding proteins in order to control its function and half-life across the human tissues. This is because IGF-1 and IGFBP-3 levels are typically in balance [20]. It is hypothesized that endogenous IGF-I may function as a stimulatory metabolic signal to the pubertal ovine hypothalamo-pituitary axis because exogenous IGF-I has been found to stimulate luteinizing hormone (LH) secretion. In adults, FSH and testosterone promote IGFBP-3 proteolysis to improve IGF-1 activity for maturation of germ cells, which may not be the case in the age group included in this study [14].

4- Conclusion

From the results of the current study, it can be concluded that the levels of GH as well as the levels of IGF-1 and IGFBP-It have significant difference between the NGHD and the patients' group , also the levels of LH, FSH and testosterone hormones among the studied groups have high significant difference ,in addition it's found that Insulin- like growth factor 1 and insulin like growth factor binding protein are highly correlated growth hormone , luteinizing hormone, and follicular stimulating hormone while testosterone were highly associated with the level of growth hormone ,finally it seems that measurement of Growth hormone alone is not enough to diagnose or exclude the disease of growth hormone deficiency and should be coupled with other parameters.

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هرمون النمو وعامل النمو الشبيه بالانسولين والبروتين الرابط لعامل النمو الشبيه بالانسولين وبعض الهرمونات في الاطفال العراقيين الذين يعانون من نقص هرمون النمو

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الخلاصة

عامل النمو شبيه الانسولين–١ له دورفي التمثيل الغذائي والنمو في جميع أنحاء الجسم وهو يرتبط بقوة وينظم بواسطة هرمون النمو، ويتم إنتاجه من قبل أي نوع من الأنسجة تقريبا، وخاصة الكبد ليكون هرمون النمو المرتبط بالبروتين الذي يزيد من نصف عمره. هدفت الدراسة إلى قياس عامل النمو شبيه الأنسولين–١ في مرضى نقص هرمون النمو وإيجاد علاقة مع المعلمات الأخرى المدروسة. تمت دراسة ١٨٠ موضوعا في المركز الوطني لمرضى السكري للعلاج والبحوث / جامعة المستنصرية في بغداد / العراق للفترة من نوفمبر ٢٠٢١ إلى أبريل ٢٠٢٢. تم سحب الدم والتحقيق فيه لمستويات IGF–1 و IGFBP–3 و LH و FSH والتستوستيرون وتم إجراء تحليل إحصائي للعثور على أي ارتباطات. لم يتم ايجاد تأثير للجنس على مستويات جميع المعلمات. عامل النمو شبية الانسولين–١ وجد له ارتباط ايجابي مع العمر ومؤشر كتلة الجسم وعامل النمو شبيه الانسولين الرابط بالبروتين –٣. بينما عامل النمو شبيه الانسولين الرابط بالبروتين–٣ وجد له ارتباط ايجابي مع مستويات عامل النمو شبية الانسولين –١ وهرمون المحفز للحوصلة والهرمون المنشط للجسم الاصغير والتستيسترون.

الكلمات الدالة: عامل النمو شبيه الانسولين –١، عامل النمو شبيه الانسولين الرابط بالبروتين–٣.