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ABSTRACT

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CORRELATION BETWEEN ASPROSIN AND SPEXIN LEVELS IN IRAQI CHILDREN WITH GROWTH HORMONE DEFICIENCY

Introduction: Growth hormone deficiency (GHD) is an endocrine disorder that causes a reduction in the synthesis of growth hormone (GH) in children, leading to short stature and delayed puberty. Insulin-like growth factor-I (IGF-1) plays a critical role in the growth-promoting effect of GH. IGF-1 levels provide information about the body’s natural release of GH. Asprosin (ASP) is a modernly recognized adipokine produced from adipose tissue linked to metabolic disorders like obesity and diabetes. Spexin (SPX) is a newly discovered adipokine implicated in various homeostatic functions, including metabolism, endocrine processes, and GH production. This study suggests a special relationship between GH, ASP, and SPX in GHD children.

Methods: investigates the potential correlation between ASP and SPX in 90 children, 40 with GHD, and 50 healthy controls. Levels of growth hormone, insulin-like growth factor-1, and vitamin D3 were measured in both groups. SPX and ASP levels were measured by using enzyme-linked immunoassay.

Results: biochemical parameters between the patient and control group showed significant differences in Hb, Vit.D3, ASP, SPX, and GH $p < 0.050$, In the correlation study, GH showed a significant negative correlation with ASP, SPX, and Hb ($p = 0.015$, $p = 0.000$ and $p = 0.024$ respectively), but show a positive correlation with D3.

Conclusion: ASP could be one of the underlying factors contributing to GHD through influencing metabolic processes linked to GH regulation. Also, differences in SPX levels may play a role in the etiology of GHD, as SPX is proven to be expressed in all endocrine glands.

Keywords: Asprosin; Spexin; GHD; IGF-1; Iraqi children.

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INTRODUCTION

Growth hormone GH is an anabolic hormone also known as somatotropin, secreted from pituitary glands [1], and responsible for regulation of several body metabolic aspects such as homeostasis of glucose, fat oxidation, and mobilization, also it allows the synthesis of proteins and cell proliferation, including tissue and body growth [2]. Several metabolic stress situations are associated with increased GH secretion, including increased blood sugar [3].

Growth hormone deficiency (GHD) is an endocrine disorder that causes a reduction in the synthesis of GH-dependent hormones and growth factors like insulin-like growth factor (IGF-I, IGF-II) and binding proteins [4]. Children with GHD have adequate body proportions when compared with others of the same age and sex, although they are generally chubbier, shorter, and appear younger than their age [5, 6], GHD may be congenital or acquired also may be related or isolated with other hormone of pituitary hormones deficiency [7].

Insulin-like growth factor-I (IGF-1) is a hormone produced by the liver in response to GH; it plays a critical role in the growth-promoting effect of GH. The IGF-1 levels may provide information about the body's natural release of GH. IGF-I in general is stable throughout the day [8], and this can be used as an indicator of GH status in children; for example, low IGF-I levels may be a sign of reduced GH production. In general, IGF-I low levels are considered a positive indication of GHD. However, various factors can affect the level of IGF-I, such as age, puberty, chronic disease, malnutrition, and GHD [9, 10].

Asprosin (ASP) is a novel adipokine that recently joined the newly established protein hormone subclass caudamin [11] produced and released by white adipose tissue. Asprosin was first discovered at Baylor College of Medicine by Romere *et al.* in 2016 while examining individuals with an inherited rare disorder named neonatal progeroid syndrome (NPS) [12]. The first target for ASP is the olfactory 734 (olfr 734) receptor that stimulates the liver for glucose production and release [12, 13].

Research performed by Liu *et al.* in 2020 [14] has shown that ASP attaches to the central OLFR734 receptor and facilitates appetite by improving olfaction and triggering AgRP neurons. Several clinical examinations have shown that ASP levels in serum have risen in patients with metabolic disorders, for instance, polycystic ovary syndrome (PCOS), obesity, type 2 diabetes, and thyroid dysfunction [15-18]. In 2020, research in China revealed that serum ASP levels in acromegaly patients are lowered, which may be related to increased blood glucose and reduced body fat mass caused by long-term exposure to high GH levels [19]. Moreover, in 2022, Mohammed *et al.* found that ASP may be one of the underlying causes of GHD through its indirect role in releasing GH [20] as the arcuate nucleus of the hypothalamus contains AgRP neurons activated by ghrelin and ASP. ASP deficiency reduces these neurons' responsiveness to ghrelin. Insulin-resistant individuals and mice have elevated asprosin levels, which also cause β-cell dysfunction and apoptosis, while reducing skeletal muscle insulin sensitivity through inflammation [21–23].

Spexin (SPX) is a novel peptide belonging to the galanin/kisspeptin family and was first known by bioinformatics before the purification/function of its protein studies. It's a developed peptide highly conserved among different craniate classes. Based on studies in vertebrates (mammalian and fish) at the tissue level found that SPX was widely scattered, released into the circulatory system, and identified at notable levels in central and peripheral tissues of the nervous system and previous study confirmed that SPX has a numerous function in different organ [24] including the heart, bones, digestion, urinary tract, reproductive organs, hormones, and brain [25].

Many studies suggest that SPX may act as a neuroendocrine signal with pleiotropic functions [26]. SPX has reported different functions in mammals, including the movement of the digestive tract, energy equilibrium, loss of weight, intake of fatty acids, and homeostasis of glucose, kidney, and cardiovascular functions. Recently, found that SPX also plays a role in the reproduction and the control of feeding in fish models [27] as SPX inhibits Luteinizing Hormone (LH) release [28]. Research indicates that estrogen treatment reduces SPX expression in the hypothalamic nuclei of spotted scat [28], while direct SPX administration increases gonadotropin-inhibitory hormone (GnIH) and gonadotropin-releasing hormone (GnRH) production in the brain, but decreases growth hormone and follicle stimulating hormone (FSH) levels.

Several studies found that BMI may affect both ASP and SPX levels. Children with high BMI have low levels of both ASP and SPX [29, 30]. As GH, ASP, and SPX are regulatory parameters that play a significant role in the growth, food intake, glucose level, and a number of body metabolisms; thus, the study aimed to investigate the potential correlation between ASP and SPX in children with GHD disorder, different in age and sex.

MATERIALS AND METHODS

1.1. Patients

This study was designed as a case-control study. The period of this study was from October 2023 to December 2023. This work was done at the National Diabetes Center/ Mustansiriyah University in Baghdad, Iraq. 40 patients (22 males and 18 females) with GHD (before treatment) were compared to 50 (25 males and 25 females) healthy children (normal BMI and normal GH levels), ages ranging from 4 to 14 years old. Furthermore, this study received ethical approval from the ethics committee of the National Diabetes Center at Mustansiriyah University in September 2023, ensuring compliance with the principles outlined in the 1964 Declaration of Helsinki and any subsequent revisions or comparable ethical standards.

1.2. Methods

Body mass index (BMI) was calculated using the formula BMI = weight (kg)/height (m^2). Venous blood samples were obtained from the controls and patients using a disposable syringe (10 mL), put in a gel tube, and centrifuged for 10 min at 3000 rpm to obtain serum. The serum is transferred into the Eppendorf tube and stored at -20 °C until analysis.

Levels of growth hormone (GH) and insulin-like growth factor-I (IGF-I) were measured by using the diaSorin analyzer device- Italy (Liaison hGH kit- Italy), (Liaison IGF-1 kit- Italy), respectively, while vitamin D was tested by the VIDAS device- France (VIDAS VITD kit- France).

The levels of ASP and SPX in the patients and control groups were determined by using BT lab enzyme-linked immunosorbent assay (ELISA) kits and following the manufacturer's instructions.

- **Exclusion criteria**

The following were the exclusion criteria

- Any subject with diabetes mellitus or other chronic diseases.
- Any subject with autoimmune diseases.
- Any subject with other endocrinopathies.

2. Statistical Analysis

Statistical data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 26.0 (SPSS Inc., Chicago, IL, USA) software program. The Shapiro–Wilk test was used to determine parametric or non-parametric analyses; all variables (except IGF-1) were determined to have a non-parametric distribution. Thus, the Mann-Whitney U-test was used to evaluate the level of significance between the patient and control groups. Results are presented as median, minimum, and maximum. The Spearman test was used for correlation. The result was considered statistically significant if the p-value was below 0.05.

RESULTS

Forty children with growth hormone deficiency (GHD) and fifty healthy male and female children were enrolled in this study. The age distribution was 4 to 14 years.

The BMIs for both groups are shown in Table 1.

Table 1: Biochemical parameters between patients and control

Metabolite	Control (median, Min–Max)	Patient (median, Min–Max)	p-value
ASP (ng/mL)	4.1 (3.12-5.21)	5.7 (2.28-17.79)	p = 0.000
SPX (pg/mL)	762.5 (714-870)	1211.5 (1017-2577)	p = 0.000
GH (ng/mL)	7.95 (6.9-19.1)	0.28 (0.1-3.5)	p = 0.000
IGF-1 (ng/mL)	183 (25.38-541)	196 (47-396)	p = 0.760
BMI (Kg/m2)	18.61 (12.25-21.33)	16.56 (9.6-31.64)	p = 0.172
D_3 (ng/mL)	11.4 (8.3-17.8)	10.65 (8.1-17.64)	p = 0.015
Hb %	10.65 (9-13.3)	12.1 (9.1-14.8)	p = 0.026

Biochemical parameters between the patient and control group showed significant differences in Hb%, D3, SPX, ASP, and GH (all p< 0.050). All study parameters – medians, minimum value, maximum value, and p-values – are shown in Table 1.

In the male group SPX, ASP, GH, and Hb% showed significant differences (all p<0.050) between patients and control while in the female group ASP and Hb% didn't show any significant value but SPX, GH, and D3 (p< 0.050) showed significant differences all study parameters medians, minimum, maximum and p-Values are shown in Table 2.

Table 2: Biochemical parameters between patients and control in male and female group

Metabolite	Male			Female		
	Patients N = 22	Control N = 25	P Value	Patients N = 18	Control N = 25	p-value
ASP (ng/mL)	5.84 (3.45-17.79)	4.09 (3.12-5.21)	0.008	5.35 (2.28-12.81)	4.13 (3.12-5.02)	0.068
SPX (pg/mL)	1241 (1017-2577)	761 (732-823)	0.000	1182 (1051-1987)	766 (714-870)	0.000
GH (ng/mL)	0.21 (0.09-6-2.7)	8.1 (6.9-10)	0.000	0.4 (0.01-3.5)	7.9 (6.9-19.1)	0.000
IGF-1 (ng/mL)	203 (47-396)	179 (70-253)	0.467	155 (61-270)	183 (52.38-541)	0.634
BMI (Kg/m2)	16.6 (9.6-31.64)	17.3 (16.5-20.8)	0.341	16.31 (13.64-27.83)	18.27 (12.25-21.3)	0.104
D_3 (ng/mL)	11.3 (8.1-17.64)	11.3 (9.4-15.3)	0.424	9.8 (8.1-13.5)	11.9 (8.3-17.8)	0.011
HB %	12.3 (9.5-14.8)	11.9 (9.5-13.2)	0.031	11.5 (9.1-12.9)	10.3 (9-13.3)	0.148

Note: N = Number of children

Correlation between ASP and SPX

The results showed a significant positive correlation between serum ASP and SPX ($r = 0.381$, $P < 0.05$) (Table 3).

Also in the correlation study, GH showed a significant negative correlation with SPX, ASP, and Hb ($r = -0.767$, $r = -0.312$, and $r = -0.238$, respectively) ($p = 0.000$, $p = 0.015$, and $p = 0.024$, respectively) but a positive correlation with D3 ($r = 0.291$, $p = 0.005$). IGF-1 showed a significant positive correlation with weight and BMI ($r = 0.255$ and $r = 0.266$, respectively) ($p = 0.050$ and $p = 0.040$, respectively). SPX, in addition to its correlation with GH, also showed a significant positive correlation with ASP and Hb ($r = 0.381$ and $r = 0.333$, respectively) ($p = 0.003$ and $p = 0.001$, respectively). Hb, in addition to its correlation with GH and SPX, showed a significant positive correlation with D3 ($r = 0.291$ and $p = 0.005$) (Table 3).

DISCUSSION

This study represents the first study assessing the correlation between ASP and SPX levels in GHD Iraqi children. A cohort of forty children, both genders, diagnosed with GHD and aged between 5 and 14 years, participated in this research.

Generally, children diagnosed with GHD exhibit elevated levels of ASP, SPX, IGF-1, and Hb, except for D3, which is found to be lower compared to the levels in control children, as indicated in Table 1. Measuring Hb (hemoglobin) and vitamin D3 levels in children with growth hormone deficiency is crucial because it helps assess overall health and growth potential. Low hemoglobin can indicate anemia, which may exacerbate growth issues, while adequate vitamin D3 is essential for bone health and metabolic processes. Monitoring these levels allows for early intervention and tailored treatments to support optimal growth and development.

Interestingly, BMI showed no significant difference between patients and controls, but the mean value in the patients was lower than that of the controls, and according to the BMI calculator, the patients' mean was classified as underweight.

In this research, the fasting ASP concentrations in patients were higher relative to the controls, contrasting with the findings of Al-Jubawi *et al.* [30], which demonstrated a notable reduction in ASP levels among children suffering from GHD in comparison to the control group. The differences observed among the studies are remarkable and highlight the necessity for additional subgroup analyses within patient samples to elucidate the true relationship between ASP and GH. Furthermore, Corica et al. (2021) [31] and Long et al. (2019) [32] propose that fasting ASP levels decrease in obese children. These findings underscore the intricate role of ASP in energy metabolism.

Despite this research finding that indicated patients with a lower body mass index exhibited higher levels of fasting SPX when compared to the control group. While another study has noted that SPX levels were significantly lower in obese children when compared to children with normal BMI [33, 34], this study showed no significant correlation between SPX and BMI; this may be due to the sample size and the wide age range.

Table 3: Correlation results between study parameters

		Weight	Height	BMI	GH	IGF-1	ASP	SPX	Hb	D3
Weight	r	1	.379**	.468**	-0.049	.255*	0.096	0.062	0.198	0.082
	p		0	0	0.649	0.05	0.468	0.564	0.062	0.44
Height	r	.379**	1	.234*	0.172	-0.094	-0.041	-0.169	0.029	.254*
	p	0		0.027	0.105	0.474	0.754	0.11	0.789	0.016
BMI	r	.468**	.234*	1	0.171	.266*	-0.025	-0.19	-0.147	0.188
	p	0	0.027		0.107	0.04	0.847	0.072	0.168	0.077
GH	r	-0.049	0.172	0.171	1	-0.081	-.312*	-.767**	-.238*	.291**
	p	0.649	0.105	0.107		0.536	0.015	0	0.024	0.005
IGF-1	r	.255*	-0.094	.266*	-0.081	1	-0.121	0.09	0.104	-0.138
	p	0.05	0.474	0.04	0.536		0.359	0.495	0.431	0.295
ASP	r	0.096	-0.041	-0.025	-.312*	-0.121	1	0.381**	0.134	-0.042
	p	0.468	0.754	0.847	0.015	0.359		0.003	0.307	0.752
SPX	r	0.062	-0.169	-0.19	-.767**	0.09	.381**	1	.333**	-0.183
	p	0.564	0.11	0.072	0	0.495	0.003		0.001	0.084
Hb	r	0.198	0.029	-0.147	-.238*	0.104	0.134	0.333**	1	.291**
	p	0.062	0.789	0.168	0.024	0.431	0.307	0.001		0.005
D3	r	0.082	.254*	0.188	.291**	-0.138	-0.042	-0.183	.291**	1
	p	0.44	0.016	0.077	0.005	0.295	0.752	0.084	0.005	

*Significant level < 0.05
**Significant level < 0.01

Additionally, this research indicated no significant difference in IGF-1 levels between the patient group and the control group. However, the patient group exhibited higher IGF-1 levels, which contrasts with earlier findings [10, 35]. It is important to mention that none of the children in the patient group received growth hormone therapy at any point during this study. This discrepancy may be influenced by factors such as the age range of the samples in this study or the duration of growth hormone deficiency. Consequently, this study suggests that relying solely on IGF-1 levels for diagnosing GHD may not be advisable.

When comparing patients to control groups of both male and female children, it was observed that only SPX and GH demonstrated a significant variance across all examined groups. However, within the male subgroup, notable differences were found in ASP and Hb levels, while in the female subgroup, a significant variance was observed only in D3 levels.

The analysis shows that there is a significant negative correlation between GH, ASP, SPX, and Hb, with p-values of 0.015, 0.000, and 0.024, respectively. On the other hand, GH is positively correlated with D3, as indicated by a p-value of 0.005. Additionally, IGF-1 shows a significant positive correlation with both weight and BMI, with p-values of 0.050 and 0.040, respectively. SPX, in addition to its correlation with GH, also showed a significant positive correlation with ASP and Hb (0.003, 0.001, respectively). Hb, in addition to its correlation with GH and SPX, showed a significant positive correlation with D3 (p = 0.005).

The relationship between fasting ASP and the analyzed parameters appears to be weak across the examined groups. This could relate to factors such as the ages of participants, sample size, and GHD duration. Further research is necessary to learn the interplay between GH, SPX, and ASP, given their significant influence on appetite, metabolites, glucose balance, and growth in children.

The outcomes presented above indicate that fasting SPX impact varies across different groups, having positive, negative, or insignificant associations with various parameters. Consequently, alterations in SPX concentrations can result in both beneficial and detrimental conditions in children's bodies (systems). This is because SPX is recognized as a novel peptide linked with several metabolic disorders. Moreover, an elevation in serum SPX levels is associated with glucose metabolism and immune functionality, according to [33].

Overall, vitamin D3 levels were found to be low in both the patient and control groups; however, it was significantly higher in the control group ($p = 0.015$). In the study examining the correlation, vitamin D3 displayed a positive correlation with growth hormone (GH) levels ($p = 0.005$). These findings are consistent with those reported by Alkubaisi *et al.* in 2020 [36], which indicated a significantly lower level of vitamin D3 in children with growth hormone deficiency (GHD) compared to their healthy counterparts ($P<0.001$).

CONCLUSIONS

Asprosin and Spexin's role in children with GHD is not well defined yet, because of the limitations of the previous studies. ASP shows no significant correlation with BMI ($p = 0.847$) between GHD children and normal children. But ASP levels are higher in GHD patients and have significant differences ($P < 0.05$), and it could be one of the underlying factors contributing to GHD. More research is needed to further explain the association between ASP, food intake, and metabolism. Also, SPX showed no significant correlation with the BMI ($p = 0.072$) and had higher levels in GHD children with a significant difference ($p = 0.000$). These differences may play a role in the etiology of GHD, as SPX is proven to be expressed in all the endocrine glands. The results reveal that GHD children have higher levels of ASP, SPX, IGF-1, and Hb. While Vit. D_3 was reduced in GHD patients as compared to healthy controls. Significant negative correlation between GH and SPX, ASP, and Hb, while D_3 shows a positive correlation with GH.

PROSPECTS FOR FUTURE RESEARCH

Further research with larger participants is needed to understand the GHD disorder and to enhance diagnostic and therapeutic approaches for GH. Also, this study suggests that the levels of ASP and SPX may be related to BMI or to the level of accelerated fat in the body, so further studies needed for ASP, SPX, BMI, Celiac screen for Celiac disease, consanguineous marriage, and lipid profile.

AUTHOR CONTRIBUTIONS

G.S. G. and L. A.G. conceived and designed the work. L.A.G., K.G., and A.L.H. performed experiments, data processing and collection. K.G. and G.S.G. analyzed and interpreted the results. L.A.G. and K.G. prepared the manuscript draft and did the statistical analysis. A.L.H. and L.A.G. edited the article. W.A.H. provided supervision and approved the final version to be published.

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CONFLICT OF INTEREST

The authors declared no conflicts of interest with respect to the authorship and publication of this article.

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ARTIFICIAL INTELLIGENCE DISCLOSURE

The authors confirm that no artificial intelligence (AI) technologies were used during manuscript writing or editing.

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