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ORIGINAL PAPER/GYNECOLOGY

Levels of a novel metabolic marker, spexin in patients with hirsutism: metabolic syndrome risk in idiopathic and polycystic ovarian syndrome (PCOS) hirsutism

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ABSTRACT

Objectives: Polycystic ovarian syndrome (PCOS) disease the most common endocrinopathy among reproductive age women , and its association with metabolic syndrome is investigated in many reports. The most common cause of hirsutism worldwide is considered to be idiopathic hirsutism (IH) defined as clinical hirsutism without underlying hormonal imbalance. Spexin is a novel peptide and is mainly involved in energy homeostasis and, has not yet made its way into clinical practice. We aim to investigate spexin in an understudied population of hirsute patients.
Material and methods: This prospective case-control study analysis involved 48 patients with hirsutism.and, was further divided into two groups: 26 had PCOS syndrome and 22 had IH. 40

healthy, age and BMI-matched non-hirsute women enrolled as the control group. The spexin level was determined using a human spexin ELISA kit.

Results: There was no statistically significant difference in spexin levels found between hirsutism and control patients 1514 vs 1425 ng/L, ($p = 0.849$). Spexin levels were found to be significantly higher in the PCOS hirsutism group than in the IH group (1668.5 ng/L vs 1021 ng/L), ($p = 0.022$). Correlations of spexin levels with total testosterone, low-density lipoprotein, and total cholesterol were found in hirsutism patients.

Conclusions: Our findings conclude that both IH and PCOS hirsutism patients have an increased risk of metabolic syndrome; hyperandrogenemia and dyslipidemia contribute to the progression of upcoming research on metabolic syndrome. Low spexin levels in IH in hirsute patients Could potentially elucidate the pathogenesis of the condition, consequently assisting in diminishing the risk of associated complications.

Key words: polycystic ovary syndrome (PCOS); spexin; hirsutism; idiopathic hirsutism (IH)

INTRODUCTION

Hirsutism defined as the presence of terminal hair in male-like patterns and, occurs in 5–15% of women [1]. The primary cause of hyperandrogenemia in females is polycystic ovarian syndrome (PCOS), with numerous studies establishing its link to metabolic syndrome [2–4], which is characterized by an inflammatory state and increased secretion of chemokines, interleukins, and adipokines [2]. Studies evaluating the attenuation of hirsutism components on metabolic syndrome risk in PCOS patients are sparse with conflicting results [5, 6], but the components of hyperandrogenemia have been consistently identified as significant predictors of metabolic disorders in a multitude of scientific investigations [5, 7–9].

The most common cause of hirsutism worldwide is considered to be idiopathic hirsutism (IH). In a recent study, a link between dyslipidemia, insulin resistance, and obesity with IH was found [10]. However, research examining the relationship between metabolic syndrome and insulin resistance in IH patients yields conflicting findings [11–13], but overall metabolic outcomes were found to be similar in women with IH and controls.

Spexin is a novel peptide involved in the regulation of energy homeostasis, body weight and metabolism. The physiological significance of spexin largely remains obscure, while investigations have elucidated the gene encoding spexin to be the most downregulated gene in

subcutaneous and omental human fat [14]. Previous animal studies have reported that spexin attenuates deleterious effects in metabolic syndrome-induced rats and that spexin induces weight loss with diet-induced obesity in rodents [15, 16]. Studies in humans regarding spexin are sparse, and it has mainly been studied in adolescents with obesity [17–19]. Lower spexin levels were found in obese individuals than in their lean counterparts. A few studies have analyzed spexin in adults, mainly in patients with insulin resistance and obesity [20–23].

Several studies have explored circulating spexin levels in women with hirsutism or PCOS, offering insights into its potential relevance to the pathophysiology of these conditions. A consistent finding across these studies is a significant decrease in spexin levels among women with hirsutism compared to controls without hirsutism. Moreover, lower spexin levels have been associated with markers of insulin resistance, hyperandrogenism, and metabolic dysfunction, suggesting a potential link between spexin dysregulation and the development or exacerbation of hirsutism. The present study, therefore, aims to compare metabolic syndrome markers and spexin in hirsutism patients with controls and give insight into the etiopathogenesis of hirsutism.

MATERIAL AND METHODS

Study population

This prospective case-control study, conducted between January 2020 and January 2021, recruited 48 consecutive patients referred with a primary diagnosis of hirsutism to the Department of Obstetrics and Gynaecology at Istanbul Teaching and Research Hospital. The hirsutism group, composed of reproductive-age women, was further divided into two subgroups: 26 with PCOS and 22 with IH. Polycystic ovarian syndrome diagnosis followed the revised Rotterdam European Society of Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM) criteria, [24] with exclusion criteria including congenital adrenal hyperplasia, Cushing's syndrome, thyroid disorders, androgen-secreting tumours and severe hyperprolactinemia.. The clinical hirsutism group was defined as patients with a modified Ferriman-Gallwey (mFG) score of 8 or higher [25]. Idiopathic hirsutism was characterized by hirsutism (mFG score ≥ 8) with normal menstrual cycles and serum androgen levels within reference values [26]. The control group comprised 40 healthy, reproductive-aged women matched for body mass index (BMI) and age, who did not exhibit hyperandrogenism or signs of hirsutism.

Biochemical and hormonal tests were conducted on morning venous blood samples collected during days 3 to 5 of the menstrual cycle, serum samples underwent centrifugation at 2000–3000 rpm at 4°C for 20 minutes. Subsequently, the separated serum samples were frozen at –80°C until they were assayed. Spexin levels were determined using a human spexin ELISA kit (Cat. No E3507Hu, Bioassay Technology Laboratory, Shanghai, China), with measurements performed in accordance with manufacturer specifications.

All specimens were obtained subsequent to the acquisition of written consent forms (endorsed by the Local Ethical Research Committee on 20.12.2019, under acceptance number: 2114) from all participants involved, including both cases and controls.The clinical investigations were carried out according to the Declaration of Helsinki.

Statistical method

Power and sample size were calculated with G*Power version 3.1.9.2. SPSS 26.0 (IBM Corporation, Armonk, New York, United States), and Medcalc 14 (Acacialaan 22, B-8400 Ostend, Belgium) programs were used in the analysis of variables. The Shapiro-Wilk Francia test was used to determine the suitability of univariate data to normal distribution, while variance homogeneity was evaluated with the Levene test. Bootstrapping was used together with independent samples t-test results, while the Mann-Whitney U test was used together with Monte Carlo results to compare two independent groups according to quantitative data. Kendall's tau b test was used to examine the correlations of quantitative variables with each other. Cut-off values were calculated according to the spexin level of the groups and the actual classification, specificity, sensitivity and accuracy rates were analyzed and expressed by receiver operating curve (ROC) curve analysis. Variables were analyzed at a 95% confidence level, and a p-value of less than 0.05 was considered significant.

RESULTS

Table 1 outlines the principal characteristics of the two cohorts. Within the demographic dataset, statistically significant differences between the studied groups were identified for follicle-stimulating hormone (FSH) 7.5 (6.4/9.9) vs 7.8 7 (5.9/8.44) mIU/mL, ($p < 0.001$), there was no statistically significant difference in spexin levels found between hirsutism and control patients 1514 (785.8/2883) vs 1425 (839.4/2556) ng/L, ($p = 0.849$) (Tab. 1).

Spexin levels were found to be significantly higher in the PCOS hirsutism group than in the IH group (1668.5 ng/L vs 1021 ng/L), ($p = 0{,}022$) (Fig. 1).

Figure 1 shows and compares the area under the curve (AUC) values of spexin. In a subgroup analysis of hirsutism patients, the area under the ROC curve was 0.68 for spexin levels ($p = 0.022$). For the cut-off value of 1046 ng/L, the accuracy rate of spexin levels was 71.1%. Receiver operating curves were also used to determine the ability of spexin to predict PCOS hirsutism (Fig. 2).

Correlations of metabolic parameters with spexin were found between total cholesterol ($r = –0{,}352$, $p < 0.001$), LDL ($r = –0.306$, $p < 0.001$) and TT ($r = 0.216$, $p = 0.011$). No correlations were found between spexin levels with BMI, age, triglyceride, high-density lipoprotein (HDL), anti-mullerian hormone (AMH), HgA1C, and fasting glucose levels in hirsutism patients (Tab. 2).

DISCUSSION

In our study, multiple hormone and metabolic parameters were investigated with metabolic marker spexin, and levels were not different between the groups. We found no difference in spexin levels between hirsutism and control subjects but spexin levels were found to be significantly higher in the PCOS hirsutism group than in the IH group. In addition, the direct relationships between spexin and plasma LDL, total cholesterol, TT, and dehydroepiandrosterone sulfate (DHEA-SO4) levels suggest that increased dyslipoproteinemia and hyperandrogenism contribute to increased metabolic syndrome risk in hirsutism patients.

Hirsutism is an endocrine disorder that is not life-threatening but does have long-term health consequences, including cardiovascular and metabolic disturbances, coupled with an adverse impact on psychological well-being. Therefore, it is important to evaluate the novel marker spexin as having a possible role in the hypothalamic gonadal axis apart from its role in energy metabolism. There have been a limited number of studies on spexin levels in PCOS patients [27–29]. In line with our study results, Beyazıt et al. [27] found that serum spexin levels did not differ between PCOS and healthy subjects, and Guler et al. [28] found low levels of spexin in PCOS patients. To date, the correlation of spexin with androgenic hormone parameters has been studied in only one study [28]. An inverse association between spexin and TT and the free androgen index was demonstrated in PCOS patients [28]. The positive association of TT in

hirsutism patients in our study suggested that spexin could interfere with androgenic hormone synthesis and spexin's interaction with the central nervous system suggests a possible influence on the hypothalamic-pituitary-adrenal axis and other hormonal axes involved in hair growth regulation.

Another interesting finding was low spexin levels in IH patients. There are not enough data showing whether patients with IH have a metabolic syndrome risk or an underlying aetiologic mechanism. An alteration in androgen receptor function most commonly associated with IH but also with possible underlying adrenal/ovarian dysfunction should not be overlooked. Low levels of spexin in studies are mainly associated with high leptin levels [17], the presence of T2DM [20], and higher HOMA-IR levels in nonalcoholic fatty liver patients [29]. This finding is also important because, as explained previously, PCOS patients have a higher risk of metabolic syndrome compared to IH. However, lower spexin levels in IH showed that, as demonstrated by only a few studies, IH also possesses a higher risk of metabolic syndrome. We assume that apart from the role of hyperandrogenism on metabolic syndrome risk in PCOS, clinicians should be aware of the same implications (increased metabolic syndrome, CVD and T2DM risk) in IH. Our study is of great value, because no study in the literature interprets the role of spexin in hirsutism patients.

The correlation of spexin levels with lipid parameters has resulted in conflicting data [20, 30, 31]. A negative correlation of spexin levels with LDL and triglycerides was shown in patients with T2DM [30], while no correlation was found in those patients in another study [20]. In agreement with our findings, Lin et al. [31] found a negative correlation of total cholesterol with spexin in healthy subjects. The precise mechanisms underlying the association between spexin levels and dyslipidemia remain incompletely understood and warrant further investigation. Proposed mechanisms may involve spexin-mediated effects on lipid synthesis, storage, and metabolism, as well as interactions with other metabolic pathways implicated in dyslipidemia.We hypothesized that apart from the hypothalamic-gonadal effect of spexin, a negative correlation represents an adaptation to dyslipidaemia associated with increased metabolic syndrome risk in hirsutism patients.

CONCLUSIONS

The limitations of our study deserve to be acknowledged. First, there was a small sample size of enrolled IH patients. Also, there is a gap in the literature regarding spexin, and more research is needed to validate our current findings. In our study, there are some strengths. Our study is one of the first to evaluate the relationship between hirsutism and spexin. Additionally, our study population has not been well-researched. We conducted research on hirsutism patients. Although the relationship of metabolic syndrome has attracted increasing attention in recent years, there are only a few studies involving such a population.

Both IH and PCOS hirsutism patients have an increased risk of metabolic syndrome; hyperandrogenemia and dyslipidemia contribute to the development of future T2DM and CVD risk. Considering the interaction of spexin between metabolic parameters provides data support for future research on risk factors associated with metabolic syndrome. Early intervention to try to reduce morbidity and mortality is often accompanied in such patients. Attention must be paid to the essential biological aspects of the disease with biochemical and molecular determinants, which in turn may facilitate the development of targeted therapeutic interventions aimed at modulating spexin signaling pathways.

Article information and declarations

Data availability statement

The datasets used or analyzed during the current study are available from the corresponding author N.A. on reasonable request.

Ethics statement

Samples were collected following a written consent form (approved by the Local Ethical Research Committee date: 20.12.2019, acceptance number: 2114) obtained from all studied cases and controls. The clinical investigations were carried out according to the Declaration of Helsinki.

Author contributions

N.A. and S.S. wrote the paper and analyzed data; S.S. and Y.A. review and edit the final paper; B.S.K. and N.A. provided essential materials; S.S., N. A and Y.A conducted research; S.S. performed statistical analysis; N.A. and S.S. made formal analysis; N.A. designed research and had primary responsibility for final content.

All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that they have no competing interests.

Supplementary material

None.

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Table 1. Biochemical and demographic characteristics of Hirsutism and Non-Hirsutism patients

	Non-Hirsutism (n = 40)	**Hirsutism (n = 48)**	**p value**
Age [years], median (q1/q3)	29 (22/37)	28 (27/33)	**0.219**
BMI [kg/m^2], mean (SD)	24.37 (3.37)	25.57 (4.82)	**0.362**
	median (q1/q3)	**median (q1/q3)**	
Spexin [ng/L]	1514 (785.8/2883)	1425 (839.4/2556)	0.849*
Total cholesterol [mg/dL]	150 (142/150)	184 (155/200)	**< 0.001***
Trigliceride [mg/dL]	80 (70/117)	86 (66/103)	0.905*
HDL [mg/dL]	42 (41/44)	45.5 (39/58)	0.258*
LDL [mg/dL]	81 (77/95)	120 (94/138)	**< 0.001***
HgA1C	5.2 (5/5.5)	5.3 (5.1/5.6)	0.340*
Total Testosterone [ng/dL]	40 (35/45)	42.15 (35/61.5)	0.209*
DHEA SO4 [µg/dL]	135 (90/135)	130.25 (80/236)	0.819*
AMH [ng/ml]	2.25 (0.9/4.1)	4.7 (2.4/9.1)	**0.001***
FSH [mIU/mL]	7.8 (6.75/11.2)	7 (5.9/8.44)	**0.019***
LH [mIU/mL]	6 (5/8)	5.735 (3.8/8.6)	0.832*
E2 [pg/mL]	47 (13/66)	32.5 (28.925/38.5)	0.679*
PRL [µg/L]	12.5 (9/16)	12.5 (8.8/22)	0.480*
TSH [ng/ml]	1.6 (0.9/2.4)	1.6 (1/2.69)	0.678*
Fasting glucose [mg/dL]	90 (85/96)	87 (82/94)	0.302*

BMI — body mass index; HDL — high-density lipoprotein; LDL — low-density lipoprotein; DHEA-SO4 — dehydroepiandrosterone sulfate; AMH — anti-mullerian hormone; FSH — follicle-stimulating hormone LH — luteinizing hormone; E2 — estradiol; PRL — prolactin; TSH — thyroid-stimulating hormone

Table 2. Correlation analysis of hormonal and metabolic parameters with spexin levels in Hirsutism patients

	Spexin [ng/L]	
	r	**p value**
Age [years]	–0.130	0.078
BMI [kg/m^2]	–0.150	0.060
Total cholesterol [mg/dL]	**–0.352**	**< 0.001**
Trigliceride [mg/dL]	0.027	0.795
HDL [mg/dL]	–0.063	0.541
LDL [mg/dL]	**–0.306**	**< 0.001**
HgA1C	0.041	0.712
Total Testosterone [ng/dL]	**0.216**	**0.011**
DHEA-SO4 [µg/dL]	0.063	0.436
AMH [ng/ml]	–0.066	0.383
FSH [mIU/mL]	0.112	0.150
LH [mIU/mL]	0.137	0.116
E2 [pg/mL]	–0.063	0.694
PRL [µg/L]	–0.039	0.622
TSH [ng/ml]	0.022	0.782
Fasting glucose [mg/dL]	–0.050	0.542

BMI — body mass index; HDL — high-density lipoprotein; LDL — low-density lipoprotein; DHEA-SO4 — dehydroepiandrosterone sulfate; AMH — anti-mullerian hormone; FSH — follicle-stimulating hormone LH — luteinizing hormone; E2 — estradiol; PRL — prolactin; TSH — thyroid-stimulating hormone

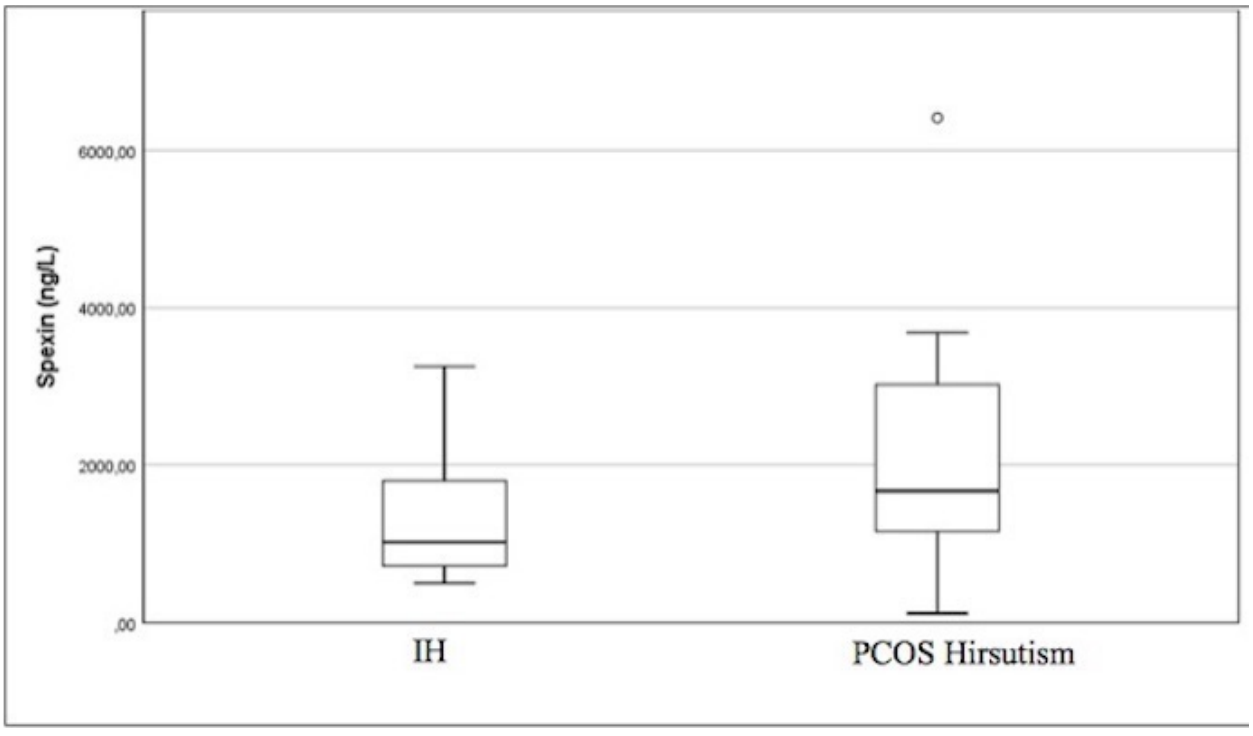

Figure 1. Spexin levels in patients with idiopathic hirsutism (IH) and polycystic ovarian syndrome (PCOS) Hirsutism

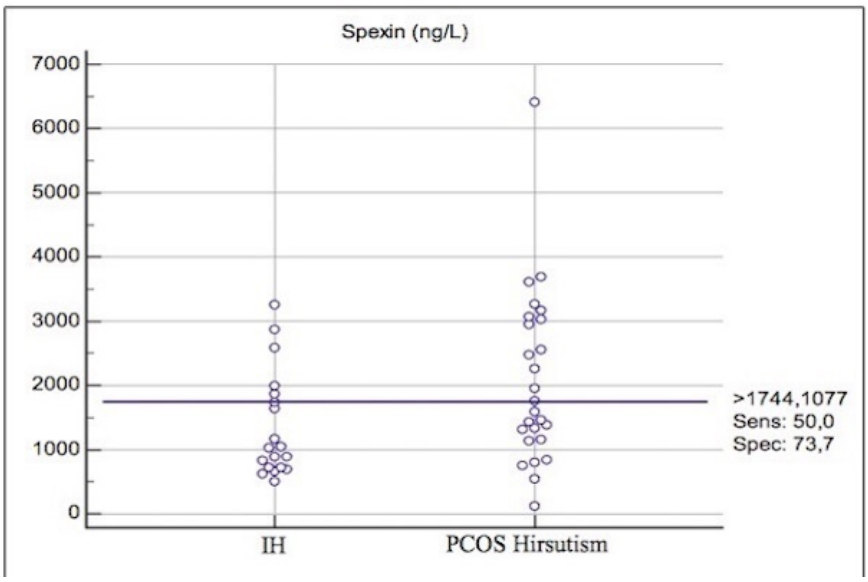

Figure 2. Discrimination analysis of spexin levels between idiopathic hirsutism (IH) and polycystic ovarian syndrome (PCOS) patients. Receiver operating curve (ROC) analysis (Honley&Mc Nell — Youden index J), AUC: Area under the ROC curve, SE: Standard Error, C.I.: Confidence interval, OR: Odds Ratio, [ss] Sensitivity, [sp] Specificity, [ppv]: Positive predictive value,[npv]: Negative predictive value, [1] n row %, [2] n column %_