European Review for Medical and Pharmacological Sciences 2023; 27: 5175-5183

Metabolic role of hepassocin in polycystic ovary syndrome

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Abstract. – OBJECTIVE: Polycystic ovary syndrome (PCOS) is a female endocrinopathy characterized by hyperandrogenemia, insulin resistance, glucose intolerance, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), and obesity. Hepassocin (HPS) is a hepatokine involved in energy and lipid metabolism. We aimed to investigate the role of HPS in metabolic dysfunction and its relationship with fatty liver in patients with PCOS.

PATIENTS AND METHODS: A total of 45 newly diagnosed PCOS patients and 42 healthy women of similar age were included in the study. Routine anthropometric, biochemical, and hormonal information were recorded. Serum HPS and high-sensitivity C-reactive protein (hsCRP) were measured, and NAFLD fibrosis score (NFS) and Fibrosis-4 (FIB-4) were calculated and correlated.

RESULTS: HPS and hsCRP values of the PCOS group were found to be significantly higher than controls (p=0.005, p<0.001, respectively). A positive correlation was found between both HPS and hsCRP and luteinizing hormone (LH) (p<0.001). No correlation was observed between HPS and NFS and FIB-4, however, only a weak negative correlation was observed between hsCRP and FIB-4. A negative correlation was found between HPS and BMI, waist circumference, fat ratio, and HbA1c (p<0.05). In multivariate regression analysis for HPS, R-squared is 0.898, and hsCRP, neck circumference, fat amount, and LH are significant factors.

CONCLUSIONS: NAFLD is an important dysmetabolic component of PCOS. Serum HPS is elevated in PCOS patients. We found a positive correlation between hsCRP and LH and a negative correlation between obesity indices, although we did not find an association between NFS and FIB-4, and HPS. In the future, large-scale molecular studies of HPS may be beneficial.

Key Words:
Hepassocin, Polycystic ovary syndrome, Hyperandrogenemia, Non-alcoholic fatty liver disease, Insulin resistance.

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrinopathy affecting ~10% of women of reproductive age[1]. Most women with PCOS have high levels of androgens and metabolic comorbidities such as insulin resistance (IR), dyslipidemia, and obesity[2]. These consequences can lead to glucose intolerance, type 2 diabetes mellitus (T2DM), hypertension, systemic inflammation, atherosclerosis, and coagulation disorders. This abnormal metabolic and hormonal environment increases the risk of non-alcoholic fatty liver disease (NAFLD), which can accompany 40-50% of women with PCOS[3,4]. Regardless of whether obese or lean, PCOS is considered to be a special risk group for NAFLD, of which 50% of patients suffer from it[5]. However, it is still unclear whether postmenopausal PCOS patients are at the highest risk for developing NAFLD[6].

NAFLD is a metabolic syndrome characterized by abnormal fat accumulation in the liver, despite the absence of alcohol consumption, and includes a spectrum of liver diseases ranging from initial stages such as hepatic steatosis and steatohepatitis to progressive stages such as cirrhosis and even hepatic carcinoma[7]. Hyperandrogenism and IR, the two main pathological components of PCOS, are associated with NALFD in recent studies[5]. However, the linkage mechanisms of PCOS and NAFLD need to be investigated. An important step in the management of NAFLD patients is to reliably exclude advanced fibrosis and prevent unnecessary biopsies using non-invasive tests such as the NAFLD Fibrosis score (NFS) or Fibrosis-4 (FIB-4)[8,9].

The liver plays an important role in the synthesis of many proteins called hepatokines, which are involved in body energy hemostasis. One of these, fibrinogen-like peptide 1 (FGL-1), also

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called hepassocin (HPS), is upregulated during hepatic regeneration and has mitogenic activity in human and rat livers[10,11]. It has been shown by Li et al[11] to protect rats from fulminant liver failure. However, decreased HPS expression was observed in patients with hepatocellular carcinoma (HCC)[12]. The structure of HPS is similar to angiopoietin-like factors (ANGPTLs) that modulate energy and lipid metabolism. Despite its protective feature in hyperglycemic crises, HPS is known to play an important role in the development of IR and NAFLD. In recent years, serum HPS levels have been found to be high in patients with T2DM and NAFLD[13,14]. In addition, there is evidence in the literature that subjects who are overweight or obese have higher levels of HPS. Moreover, it has been suggested[15] that it may be a marker for metabolic dysregulation in obesity.

HPS is a relatively new molecule and its role in various diseases such as HCC, rheumatoid arthritis, and gestational diabetes mellitus continues to be investigated[16-18]. So, in our study, we aimed to investigate the role of HPS in metabolic dysfunction and its relationship with fatty liver in patients with PCOS.

Patients and Methods

Study Population

In this prospective cross-sectional study, we included newly diagnosed PCOS patients (n=45) and healthy controls (n=42) between 18-45 years of age admitted to the Endocrinology and Metabolic Diseases outpatient clinic of Ankara Training and Research Hospital[19].

Patients with co-morbidities or taking any medication, active infection, psychiatric disease, endocrinopathy, pregnancy or lactation period, and those following a special diet were not included in the study.

Clinical Parameter Assessment

Body weight was measured on a digital scale with minimal clothing and no shoes. The height was measured using a non-stretch stadiometer. Body mass index (BMI) was calculated by dividing body weight (in kilograms) by the square of height. We measured waist circumference (WC) at the navel level with a single layer of light clothing. Also, we measured the hip circumference (HC) by measuring the distance around the widest part of the hip. We assessed hirsutism using the modified Ferriman-Gallwey score (mFGS).

We collected venous blood samples from the antecubital vein between 9:00 am and 11:00 am after overnight fasting in the resting position. We centrifuged the samples at 1,500 g for 10 minutes. The sera were separated into Eppendorf tubes and stored at -80°C until analysis. Demographic and clinical data of the subjects were recorded.

In addition to routine endocrinological tests, serum HPS and high-sensitivity C-reactive protein (hsCRP) parameters were also examined. We determined serum HPS levels with a human ELISA test Kit (Elabscience Biotechnology Inc., Houston, TX, USA) according to the manufacturer's protocol. The detection range was between 0.16-10 ng/mL, the assay sensitivity was 0.10 ng/mL. The coefficient of variation was <10%.

Also, we used Human hsCRP ELISA Kit (Elabscience Biotechnology Inc., Houston, TX, USA). The detection range was between 15.63-1,000 pg/mL and the sensitivity was 9.38 pg/mL. The coefficient of variation was <10%.

NAFLD Assessment

NFS =-1.675+0.037×age (years)+0.094×BMI (kg/m^2)+1.13×impaired fasting glucose (IFG)/diabetes (yes=1, no=0)+0.99×aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio - 0.013×platelet count (×10^9/L) - 0.66×albumin (g/dl).

The NFS was further categorized into two levels: low probability (< -1.455) and high probability (≥ -1.455)[8].

FIB-4=age (years)×AST [U/l]/(platelets [10^9/l] × (ALT [U/l])$^{1/2}$).

Cut off for FIB-4 was used as <1.30, considered low probability[9].

Statistical Analysis

The data obtained from the research were analyzed with SPSS 22 package programs (Statistical Package for Social Sciences; IBM Corp., Armonk, NY, USA). While evaluating the data, continuous variables were expressed as mean±standard deviation, standard error, and frequency data as numbers (%). Chi-square analysis (Pearson Chi-square) was applied in the categorical comparison between groups. The conformity of continuous data to normal distribution was evaluated with the Kolmogorov-Smirnov test. The Independent Samples *t*-test was used to compare the variables with normal distribution between the two groups. Pearson's correlation test was used to examine the relationship between continuous variables.

Since there was a significant difference between the groups in terms of body mass index (BMI), ANCOVA analysis was performed to adjust the BMI effect. A multiple linear regression analysis was conducted to identify variables that best predicted plasma HPS concentrations, of which the variable selection strategies were stepwise and backward. The statistical significance level in the analysis was accepted as $p<0.05$.

Results

The groups were similar in terms of age, smoking, and marital status. The anthropometric, biochemical, and hormone panels of the participants are presented in Table I.

Despite no difference between the groups in terms of NFS, there was a statistically significant difference between the two groups, with FIB-4 being higher compared to the control group ($p=0.76$ and $p=0.001$, respectively). HbA1c was similar between the two groups ($p=0.068$). However, fasting blood glucose and homeostasis model IR assessment (HOMA-IR) were higher in the PCOS group, and there was a statistical difference between the groups ($p<0.001$ and $p<0.001$, respectively). Total testosterone and dehydroepiandrosterone sulfate (DHEAS) were higher in favor of the PCOS group, and there was a statistical difference between the groups.

According to the results of ANCOVA analysis adjusted for BMI, the HPS and hsCRP values of the PCOS group were found to be significantly higher than the control group (Table II).

A positive correlation was found between both HPS and hsCRP and luteinizing hormone (LH) ($p<0.001$). A negative significant correlation was found between HPS and BMI, waist, hip, and neck circumferences, fat ratio, amount of fat, lean mass, and HbA1c ($p<0.05$). There was a negative correlation between hsCRP and FIB-4 and 17OH progesterone, and a positive correlation between hsCRP and HOMA-IR, LH, log TG, total testosterone, and DHEAS ($p<0.05$) (Table III).

In the multivariate regression analysis for HPS, the R square value was 0.898. Both the stepwise forward and backward selection strategies showed a consistent pattern, such that only hsCRP ($p=0.002$) had a significant effect according to the forward model design. In this case, it is said to be adjusted according to the others [BMI, WC, neck circumference, hip circumference (HC), fat amount, fat ratio, HbA1c, LH]. According to the backward selection design model, at the last eighth step, hsCRP ($p<0.001$), neck circumference ($p=0.003$), amount of fat ($p=0.002$), and LH ($p=0.012$) were significant parameters.

Discussion

The search for new markers or newly calculated indices such as the Visceral Adiposity Index (VAI) or NFS is used to determine the metabolic risk of patients with PCOS. PCOS is observed not only in obese patients but also in patients with normal body mass index. VAI is used to detect the existence of metabolic syndrome, and cardiac and metabolic complications[20-22]. In calculating VAI and NFS, biochemical parameters and anthropometric measurements are used. If some correlation could be found between HPS and PCOS, maybe it could also be adapted for existing or some brand-new indices. Amongst the present indices, we have used the NFS in this study.

In some recent studies[23,24], new markers are mentioned. One of the studies[23] is about Galectin-1 which is synthesized by immune cells, and found to be highly expressed in patients with PCOS. In one study carried out by Amin et al[24], the authors reported 5 novel oxytocin receptor (OXTR) variants that are significantly associated with PCOS. These recent studies[23,24] could have potential therapeutic results such as in some rat model studies[25] with oxytocin. HPS is investigated in our research for this kind of diagnostic or therapeutic improvement in PCOS.

In our study, we studied HPS, NFS, and FIB-4. We found that serum HPS levels were higher compared to PCOS patients than in healthy controls after matching BMI. There was a positive correlation between HPS and hsCRP. No correlation could be established between HPS and NFS and FIB-4. However, no correlation was found between hsCRP and NFS, while a weak but significant negative correlation was found in FIB-4.

Although obesity markers such as BMI, and WC were significantly higher in PCOS patients compared to the control group, a negative correlation was found between them and HPS, contrary to our expectations.

Total testosterone and DHEAS were higher in PCOS patients, but there was no correlation between these parameters and HPS. A positive correlation was found between LH and both HPS and hsCRP.

Table I. Clinical characteristics of study participants in each group.

Variables		PCOS (n=45)	Controls (n=42)	p
Age, years		25.2 ± 5.0	26.6 ± 4.2	0.173
Marital status, n (%)	Married	18 (40.9)	16 (38.1)	0.790
	Single	26 (59.1)	26 (61.9)	
Smoker, n (%)	Yes	8 (19.0)	6 (14.3)	0.558
	No	34 (81.0)	36 (85.7)	
USG, n (%)	Normal	9 (20.9)	-	-
	Polycystic	34 (79.1)	-	
NFS		-3.7 ± .9	-3.8 ± 1.0	0.760
FIB-4		.4 ± .1	.5 ± .1	**0.001****
BMI (kg/m^2)		28.8 ± 6.2	23.2 ± 3.9	**< 0.001****
WC (cm)		93.3 ± 14.1	81.1 ± 9.4	**< 0.001****
HC (cm)		107.3 ± 10.7	100.0 ± 8.6	**0.002****
NC (cm)		33.6 ± 2.2	31.2 ± 1.5	**< 0.001****
Fat ratio (%)		34.7 ± 8.0	26.3 ± 8.1	**< 0.001****
Fat amount (kg)		27.0 ± 10.8	17.0 ± 8.0	**< 0.001****
Lean mass (kg)		48.0 ± 4.0	44.4 ± 3.6	**< 0.001****
FBG (mg/dL)		91.7 ± 8.4	84.9 ± 6.1	**< 0.001****
HbA1c (%)		5.4 ± .3	5.3 ± .3	0.068
Fasting insulin (mIU/L)		15.5±8.5	8.6±2.9	**< 0.001****
HOMA-IR		3.8±2.1	1.8±.6	**< 0.001****
ALT (U/L)		26.0 ± 18.2	13.1 ± 6.7	**< 0.001****
AST (U/L)		19.9 ± 9.1	16.9 ± 5.3	0.062
GGT (U/L)		17.2 ± 7.1	11.9 ± 6.2	**0.001****
Creatinine (mg/dL)		.7 ± .1	.7 ± .1	0.728
eGFR (mL/min/1.73 m^2)		121.8 ± 8.0	120.2 ± 7.9	0.350
Total cholesterol (mg/dL)		175.3 ± 32.1	154.3 ± 29.2	**0.003****
TG (mg/dL)		122.2 ± 80.3	73.6 ± 31.6	**0.001****
Log TG		2.0 ± 0.2	1.8 ± 0.2	**< 0.001****
HDL (mg/dL)		52.9 ± 13.5	55.4 ± 10.2	0.351
LDL (mg/dL)		98.0 ± 25.1	84.2 ± 26.6	**0.019***
Platelet (×10^9/L)		290.1 ± 52.6	277.6 ± 59.0	0.316
Albumin (g/L)		46.5 ± 3.3	46.7 ± 2.7	0.856
TSH (mIU/ml)		2.5 ± 1.1	2.3 ± .9	0.390
Free T4 (ng/dL)		1.2 ± .2	1.2 ± .1	0.918
Anti TPO (IU/mL)		29.4 ± 70.1	18.9 ± 32.2	0.397
FSH (IU/L)		6.3 ± 1.6	6.5 ± 2.3	0.818
LH (IU/L)		11.8 ± 8.5	6.8 ± 2.3	0.317
E2 (ng/L)		54.4 ± 28.1	34.8 ± 7.3	0.339
17-OHP (ng/dl)		1.6 ± .8	2.2 ± .2	0.188
free T (ng/ml)		2.6 ± 2.5	1.3 ± .6	0.393
TT (ng/dL)		49.4 ± 17.7	27.9 ± 14.3	**< 0.001**
DHEAS (µg/dL)		375.0 ± 158.1	275.1 ± 128.9	**0.005**
mFGs		7.9 ± 4.2	-	-

Data are presented the mean ± standard deviation or number (%). **p*-value ≤0.05 denoted as statistically significant (*in bold*). ***p*-value ≤ 0.01 denoted as statistically significant. Student's *t*-test; Mann-Whitney U test were used.NFS: NAFLD fibrosis score; FIB-4: Fibrosis-4; BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; NC: Neck circumference; FBG: Fasting blood glucose; HOMA-IR: Homeostasis model assessment of insulin resistance; ALT: Alanine aminotransferase; AST: Aspartat aminotransferase; GGT: gamma-glutamyl transferase; GFR: glomerular filtration rate; TG: Triglyceride; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TSH: thyrotropin; fT4: Free T4; free thyroxine; Anti TPO: Anti-thyroid peroxidase; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; E2: Estradiol; 17-OHP: 17-hydroxyprogesterone; free T: free testosterone; TT: Total testosterone; DHEAS: Dehydroepiandrosterone sulfate; mFGs: Ferriman-Gallwey score.

In the regression analysis, hsCRP, neck circumference, amount of fat, and LH were important parameters affecting HPS.

NAFLD is a common risk factor for PCOS and is known as the hepatic manifestation of IR. It has been proven[26] to be associated with obesity, T2DM, and dyslipidemia. Elevated levels of HPS have been shown[11] to have protective effects on the liver as well as associated with the development of NAFLD. In a study by Wu et al[27] with a total of 393 subjects, NAFLD subjects had significantly higher serum HPS levels than

Table I. Comparison of hepaccosin and hsCRP values for groups when BMI matched.

	PCOS (n = 45)	Controls (n = 42)	F	p
Hepassocin (pg/mL)	4.07 ± 0.33	2.59 ± 0.34	8.488	**0.005**
hsCRP (ng/mL)	470.96 ± 30.35	245.75 ± 30.76	24.008	**< 0.001**

p-value < 0.05 denoted as statistically significant (*in bold*). ANCOVA test was used. hsCRP: high sensitivity C-reactive protein.

Table III. Correlation analysis of hepassocin and hsCRP with anthropometric and biochemical values (n = 87).

	Hepassocin		hsCRPl	
	r	p	r	p
hsCRP	**.489**	**< 0.001****		
Age	-.153	.157	.011	.918
NFS	-.170	.122	-.144	.191
FIB-4	-.093	.394	**-.242**	**.025***
BMI	**-.327**	**.002****	.153	.162
WC	**-.410**	**< 0.001****	.113	.339
HC	**-.537**	**< 0.001****	-.133	.272
NC	**-.339**	**.007****	.109	.401
Fat Ratio	**-.461**	**< 0.001****	.123	.300
Fat Mass	**-.407**	**< 0.001****	.153	.197
Lean Mass	**-.334**	**.004****	.157	.189
FBG	.099	.368	.140	.200
HbA1c	**-.270**	**.016***	.079	.484
Fasting insulin	-.174	.153	.072	.554
HOMA-IR	-.161	.164	**.238**	**.039***
ALT	-.107	.328	.172	.112
AST	-.085	.435	.043	.694
GGT	-.107	.347	.183	.106
Creatinine	-.020	.856	-.075	.493
GFR	.106	.328	.098	.368
Total cholesterol	-.067	.549	.131	.239
TG	-.170	.126	.207	.062
Log TG	-.139	.213	**.265**	**.016***
HDL	.206	.065	-.116	.302
LDL	-.039	.726	.131	.245
Platelet	-.076	.498	.182	.102
Albumin	-.022	.848	-.131	.244
TSH	-.100	.380	-.090	.431
T4	-.116	.330	.070	.557
Anti TPO	.160	.173	.185	.114
FSH	.282	.139	.307	.106
LH	**.362**	**.045***	**.455**	**.010***
E2	.155	.413	.141	.456
17-OHP	-.176	.258	**-.449**	**.003****
Free T	.331	.056	.173	.326
TT	.175	.133	**.437**	**< 0.001****
DHEAS	.088	.462	**.249**	**.035***
mFGs	-.110	.493	-.027	.865

*Correlation is significant at the ≤ 0.05 level. **Significant when $p \leq 0.01$. hsCRP: high sensitivity C-reactive protein; NFS: NAFLD fibrosis score; FIB-4: Fibrosis-4; BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; NC: Neck circumference; FBG: Fasting blood glucose; HOMA-IR: Homeostasis model assessment of insulin resistance; ALT: Alanine aminotransferase; AST: Aspartat aminotransferase; GGT: gamma-glutamyl transferase; GFR: glomerular filtration rate; TG: Triglyceride; HDL: High density lipoprotein; LDL: Low density lipoprotein; TSH: thyrotropin; fT4: Free T4; free thyroxine; Anti TPO: Anti thyroid peroxidase; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; E2: Estradiol; 17-OHP: 17-hydroxyprogesterone; free T: free testosterone; TT: Total testosterone; DHEAS: Dehydroepiandrosterone sulfate; mFGs: Ferriman-Gallwey score.

those without NAFLD. In another study[28], HPS was shown to be significantly increased in mice fed with a high-fat diet and primary hepatocytes treated with oleic acid, which provided *in vivo* and *in vitro* models of NAFLD.

The *FGL-1* gene promoter has potential binding sites of signal transducer and activator of transcription 3 (*STAT3*), and the unsaturated fatty acid activates *STAT3*, thereby increasing HPS expression. Blockade of *STAT3* dose-dependently inhibits HPS expression; this is responsible for the increased level of HPS under pro-inflammatory conditions[29]. HPS affects the phosphorylation of extracellular signal-regulated kinases (*ERK1/2*) to increase the activity of genes related to lipid synthesis, so lead to lipogenesis in hepatocytes. In contrast, in one study[27], the ERK1/2 inhibitor PD98059 blocked the expression of HPS-induced synthesis-related genes *in vitro*. HPS may be an acute reactant of liver steatosis stress and participates in hepatic lipid metabolism in an *ERK1/2*-dependent manner. HPS may therefore serve as a biomarker candidate in the pathogenesis of NAFLD and as an indicator of treatment response.

HPS, one of the hepatokines that mediates communication between the liver and skeletal muscle, also acts as a link between IR and NAFLD. As a result of the accumulation of fatty acids in hepatocytes, HPS expression increases, thus insulin signal is impaired in peripheral tissues and contributes to the development of T2DM[14]. In addition, HPS is increased in diabetic patients with or without hepatic steatosis in a study by Lu et al[30]. Induction of endoplasmic reticulum stress by HPS in organs such as skeletal muscle, adipose tissue, and liver in animal models fed with a high-fat diet supports the hypothesis that HPS suppresses *AMPK* activity and impairs insulin signaling, although its molecular mechanism remains unclear[31]. Jung et al[31] showed that although HPS increases phosphorylation of mitogen-activated protein kinases (MAPKs) such as p38, ERK1/2, and c-Jun N-terminal *kinase* (JNK), only ERK1/2 contributes to HPS-mediated hepatic IR. These variations may be due to differences between hepatocytes and skeletal muscle cells.

Examining the role of HPS in glucose and lipid metabolism, its overexpression promoted lipid accumulation *via* an *ERK1/2*-mediated pathway, whereas the inactivation of HPS reduced oleic acid-induced lipid accumulation, suggesting a causal role of HPS in the development of NAFLD[27].

On the other hand, Demchev et al[32] showed that HPS knockout mice exhibited improved hepatic gluconeogenesis and lower fasting hyperglycemia. The administration of recombinant HPS also aggravates insulin signaling to induce IR through *ERK1/2*-mediated signaling in hepatocytes[14]. However, the role of HPS in the pathogenesis of IR in skeletal muscle remains unknown. In their experiments investigating the mechanism of induction of HPS by p38 activation in hepatocytes under hyperlipidemic conditions, Jung et al[31] identified HPS as an obesity-induced hepatokine that induces IR in skeletal muscle cells *via* the *EGFR/JNK*-mediated pathway.

In our study, there was a statistically significant difference in PCOS in terms of ALT, gamma-glutamyl transferase (GGT), total cholesterol, triglyceride (TG), and low-density lipoprotein (LDL), while high-density lipoprotein (HDL) levels were similar between the two groups. The FIB-4 score was <1.3 in both groups and was within normal limits, however, the FIB-4 of the case group was found to be significantly lower than the one of the control group.

In addition, although there was no difference between the groups in terms of NFS, it was <−1.455 in both groups and was within the normal reference range. Therefore, no correlation was seen between these scores and HPS. However, while no correlation was found between hsCRP and NFS, a weak but significant negative correlation was found with FIB-4.

However, Huang et al[15], in their study, investigated the relationship between HPS and obesity, and found that HPS levels were significantly higher in overweight or obese subjects compared to normal-weight subjects. In multiple linear regression analysis, however, they[15] showed that BMI, WC, NAFLD, and HOMA-IR were independently associated with HPS after adjusting for age, gender, HDL, log TG, hsCRP, ALT, the estimated glomerular filtration rate, and systolic blood pressure.

In our study, although BMI, WC, HC, neck circumference, body fat amount, and the fat ratio of PCOS patients were significantly higher than the control group, contrary to our expectations, a negative correlation was found between these parameters and HPS, but no correlation was found with hsCRP. This may be due to the absence of severely obese patients in our study.

In their study, Abdelmoemen et al[13] showed that there was more serum HPS overexpression in the patient group with T2DM and NAFLD than the group with only diabetes and even the group

with only NAFLD. And they also concluded that HPS might facilitate increased hepatic lipid accumulation with NAFLD and T2DM.

In our study, while there was a statistically significant increase in favor of the PCOS group in terms of fasting blood glucose, fasting insulin, and HOMA-IR, HbA1c was similar between the two groups. However, a weak negative correlation was observed between HPS and only HbA1c, while a weak positive correlation was observed between hsCRP and HOMA-IR.

Ketenci Gencer et al[33], on the other hand, showed for the first time that HPS levels were higher in PCOS patients than in controls. In addition, while there was a statistically significant difference between obese and non-obese PCOS, HPS levels were found to be similar between normal weight PCOS and healthy controls. In their study, HOMA-IR was independently associated with hepassocin concentrations after adjusting for age, LDL, HDL, TG, total testosterone, DHEAS, and C-reactive protein (CRP).

Similarly, in our study, HPS and hsCRP levels were found to be significantly higher in PCOS patients. As expected, total testosterone and DHEAS were higher in PCOS patients, but there was no correlation between these parameters and HPS, whereas a positive correlation with hsCRP was present.

In patients with PCOS, sustained high-frequency gonadotropin-releasing hormone (GnRH) pulses cause an increase in the amplitude of LH pulses, resulting in excessive LH secretion and a relative absence of follicle-stimulating hormone (FSH) leading to hyperandrogenism[34]. Hyperandrogenism is an independent predictor of NAFLD in obese or lean PCOS[35]. Chronic low-grade inflammation in PCOS may be mediated by obesity and hyperandrogenism. The hypertrophy of adipocytes in PCOS causes interstitial vascular compression, resulting in inadequate perfusion and hypoxia in adipose tissue. And this stimulates and regulates nuclear factor κB (NF-κB) activation and regulates the expression of critical genes involved in the inflammatory response. This process induces the production and release of many mediators and triggers chronic low-level inflammation in the body, where IL-6 and IL-1β can also stimulate CRP synthesis in the liver[36].

In our study, although there was no difference between the two groups in terms of LH, a positive correlation was found between LH and both HPS and hsCRP, which may indicate the negative effects of LH on metabolic parameters.

Limitations of the Study

The sample size was small, the BMI was not equal between the groups, the level of hepatosteatosis could not be demonstrated by biopsy, liver imaging was not performed, tissue expression of HPS could not be detected in the simultaneous liver or ovary, and it was a cross-sectional study.

Conclusions

A growing body of evidence[5] suggests a tight link between NAFLD and PCOS. Many factors such as obesity, IR, hyperlipidemia, and nutrition may play a role in etiopathogenesis. Serum HPS, a hepatokine, is elevated in PCOS patients as well as in obesity or NAFLD. However, in our study, we could not find any correlation between non-invasive markers of hepatosteatosis such as NFS and FIB-4 with HPS in PCOS patients. We found a positive correlation between HPS and hsCRP and LH, and a negative correlation between obesity indices. It has been reported[37] that NAFLD has a causal role in the development of IR in skeletal muscle. Therefore, hepatokines can be considered potential therapeutic targets to treat NAFLD and IR. Whether HPS elevation is a cause or a consequence of PCOS and its potential can be used in therapy may be elucidated by future large-scale molecular studies in ovarian and liver tissue.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

We would like to thank the Diagen Biotechnological Systems Health Services R&D center staff for the Hepassocin and hsCRP laboratory procedure support.

Authors' Contribution

EIC: Conceptualization, formal analysis, methodology, visualization, writing, review and editing. TO: Data curation, formal analysis, investigation, Project administration, validation, writing. IT: Investigation, validation, writing, review and editing. SNF: Data curation, investigation, resources, writing, review and editing. CC: Supervision, software, writing, review and editing.

Ethics Approval

The present study protocol was reviewed and approved by the Ethics Committee of Ankara Training and Research Hospital (No.: E-19-157).

Informed Consent
Written informed consent was obtained from the participants of the study.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Funded by the researchers in the study.

Availability of Data and Materials
All data necessary to support the protocol are available upon reasonable request.

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