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The relation of dermcidin with insulin resistance and inflammation in women with polycystic ovary syndrome

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SUMMARY

OBJECTIVE: Polycystic ovary syndrome is the most common endocrinopathy among women of reproductive age. Polycystic ovary syndrome is a metabolic disorder associated with insulin resistance and subclinical inflammation. Dermcidin, an antimicrobial peptide, involves in insulin resistance and inflammatory processes. Dermcidin suppresses the secretion of insulin production from the liver/pancreas and also increases insulin resistance. We aimed to discover whether dermcidin levels were altered in polycystic ovary syndrome women compared to controls and determine the link of dermcidin with hormonal-metabolic parameters in polycystic ovary syndrome women.

METHODS: The current research was designed as a case-control study and Rotterdam 2003 criteria were used for diagnosing polycystic ovary syndrome. A total of 75 subjects with polycystic ovary syndrome and 75 age- and body mass index-matched subjects as controls were enrolled in the study. The insulin resistance state was determined using a homeostatic model assessment of insulin resistance and quantitative insulin sensitivity check index. High-sensitivity C-reactive protein levels were assessed to define inflammation.

RESULTS: Circulating dermcidin levels were measured by enzyme-linked immunosorbent assay. Dermcidin levels were significantly increased in polycystic ovary syndrome subjects compared to controls (172.53±42.41 ng/mL vs. 108.44±31.69 ng/mL, $p<0.001$). Homeostatic model assessment of insulin resistance and high-sensitivity C-reactive protein levels were markedly increased, whereas quantitative insulin sensitivity check index levels were notably decreased in women with polycystic ovary syndrome compared to controls. Linear regression analysis revealed that dermcidin exhibited an independent link with homeostatic model assessment of insulin resistance and high-sensitivity C-reactive protein, whereas dermcidin displayed an inversely independent link with quantitative insulin sensitivity check index.

CONCLUSION: Increased dermcidin levels were associated with insulin resistance and inflammation in polycystic ovary syndrome women, suggesting that dermcidin may play a role in the pathophysiology of polycystic ovary syndrome.

KEYWORDS: Polycystic ovary syndrome. Dermcidin. Insulin resistance. Inflammation.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex and heterogeneous disease, consists of both reproductive and metabolic issues, and affects 10–15% of women in their reproductive age. The disease is characterized by clinical and/or laboratory hyperandrogenism, menstrual dysfunctions, and polycystic ovaries. The pathophysiology of PCOS is not yet exactly clarified. A variety of mechanisms are considered to play a crucial role in the development of PCOS, including insulin resistance and inflammation. Insulin resistance and compensatory hyperinsulinemia affect up to 70% of women with PCOS. Besides insulin resistance, glucose and lipid metabolism disorders are common in women with PCOS, along with hypertension and obesity, and these metabolic and endocrinological disorders show variability with advancing age[1,2]. PCOS is associated with chronic low-grade inflammation. It has been reported that inflammatory markers such as C-reactive protein (CRP), pro-inflammatory cytokines, and chemokines are increased in women with PCOS[1-4]. Moreover, chronic low-grade inflammation has emerged as a key contributor to the metabolic and ovarian abnormalities, including androgen excess secretion in PCOS[1].

Dermcidin is an antimicrobial peptide that plays a crucial role in a variety of biological processes involving glucose metabolism and inflammation. Dermcidin induces insulin resistance. It was reported that dermcidin inhibited glucose uptake in the liver through the inhibition of glucose transporter type 4 (GLUT4) synthesis (Figure 1). GLUT4 is an insulin-regulated glucose transporter that mediates the uptake of glucose regulated by insulin[5]. In contrast, it was reported that dermcidin inhibited insulin secretion as well but the

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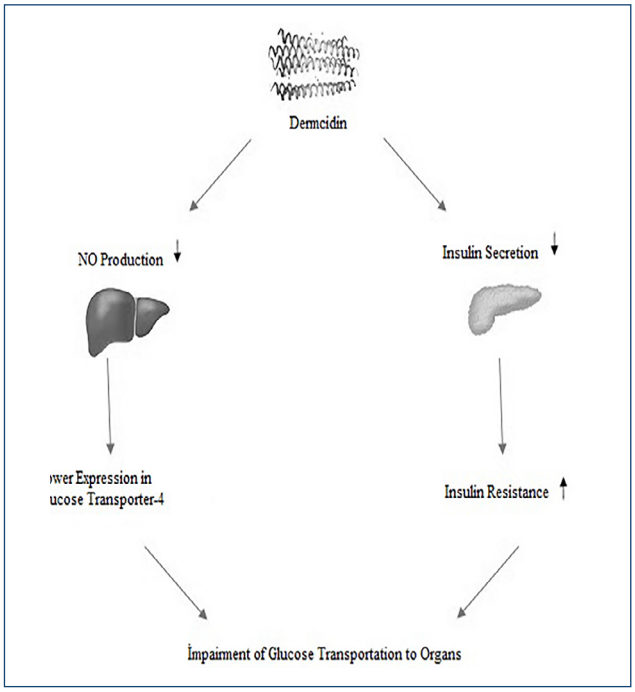


Figure 1. Effects of dermcidin on glucose metabolism.

mechanistic pathway has not yet been clarified. Additionally, it was demonstrated that dermcidin induces the synthesis of tumor necrosis factor-alpha (TNF-α)[6]. Clinical data are limited regarding dermcidin, and dermcidin levels were found to be elevated in subjects with hypertension, type 1 diabetes mellitus (T1DM), and gestational diabetes mellitus (GDM)[8-11]. Common treatment strategies in PCOS subjects are based on exercise, diet, nutrient supplementation, and treatment of insulin resistance[12]. Currently, insulin-sensitizing agents are also used to treat such patients based on their main pathophysiological substrate, hyperinsulinemia, but those treatment options are not sufficent. Therefore, we investigated dermcidin levels in women with PCOS[13].

We aimed to evaluate whether dermcidin levels were altered in women with PCOS compared to controls and evaluate whether there were any relationships between dermcidin and hormonal-metabolic parameters in women with PCOS.

METHODS

Ethics committee approval was obtained from Bozyaka Training and Research Hospital with decision number 29/05/2020-01. The written informed consent was taken from each recruited subject. The study was performed in accordance with the principles of the Declaration of Helsinki (revised in 2008).

A total of 75 PCOS subjects and 75 age- and body mass index (BMI)-matched subjects with normal menstrual cycle were recruited in this case-control study. The research was conducted between July 2019 and January 2020 in the Department of Internal Medicine, Bozyaka Training and Research Hospital.

Polycystic ovary syndrome group

Polycystic ovary syndrome subjects were selected using Rotterdam consensus criteria after excluding other causes of hyperandrogenism and ovulatory dysfunction. Although two out of three criteria are sufficient for choosing PCOS subjects, we had all the three following criteria in PCOS recognition for an appropriate homogeneity[10]: identification of oligo- and/or anovulation, identification of biochemical and/or clinical signs of hyperandrogenism, and use of the Ferriman-Gallwey [FG] for hirsutism determination[11] and occurrence of ≥12 follicles with the size of 2–9 mm in diameter or an ovarian volume of >10 mL (without a cyst or dominant follicle in either ovary) for determination of typical ultra-sonographic symptoms of polycystic ovaries as one ovary is sufficient for diagnosis. The subjects with FG score ≥8 were presented as hirsute. The biochemical hyperandrogenism was identified when testosterone (normal range: 0.52–2.42 nmol/l), and/or dehydroepiandrosterone sulfate (DHEA-S) (normal range: 10–248 µg/dl), and/or free androgen index (FAI) ≥5% of serum levels were more than the reference interval limitation[12].

Control group

The subjects were selected among women who visited gynecology or internal medical clinics for a routine checkup or who were volunteers to take part in the study by hospital employees. The subjects of the control group had normal menstrual cycles without concomitant health problems, acne, hyperandrogenism, or signs of hirsutism.

Exclusion criteria

Apart from PCOS, the subjects having the evidence of irregularity in menstrual cycles and/or excess androgen, i.e., hyperprolactinemia (<22 ng/mL), Cushing's syndrome (physical findings), non-classical congenital adrenal hyperplasia (17-hydroxy-progesterone <3 ng/mL)], thyroid disorders (0.41<TSH<4.5 µIU/mL), and galactorrhea, breastfeeding, pregnancy, decreased levels of glucose tolerance or having type 1/type 2 diabetes, familial hyperlipidemia, having a background of hypertension, suffering from liver/renal disorders or congestive heart failure, having a history of coronary artery disease, malignancy or acute infection (within 14 days), gestational diabetes mellitus, presence of any

chronic inflammatory or autoimmune disorders, undergoing treatment of hormonal contraception and/or anti-androgen (within the preceding 6 months), and not using medications for dyslipidemia, hypertension, hyperglycemia, insulin resistance, or obesity were excluded from the study.

Anthropometric evaluation

The weight (kg) and height (cmr) of subjects were measured. BMI was calculated using the following formula: BMI: weight (kg)/square meter of height (m^2). After a 15-min resting period, the blood pressure was measured while subjects were in a sitting position.

Biochemical evaluation

The venous blood samples of the subjects were obtained from the antecubital veins during the early follicular phase of menstrual bleeding (days 3–5), either spontaneous or progesterone-induced menses, in the morning following a 10-h fasting period. The blood samples were placed in room temperature for at least 30 min and allowed to clot. The clotted samples were centrifuged at 2000×g for 15 min. For analysis of neudesin, the separated serum samples were kept in aliquots at –80°C. Some dedicated kits (Abbott Diagnostics, Wiesbaden, Germany) from an auto-analyzer (Abbott Architect C 16000, IL, USA) were used to measure fasting plasma glucose (FPG), hs-CRP, total cholesterol, triglyceride, and high-density lipoprotein cholesterol (HDL-C). The low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation[13]. Chemiluminescent microparticle immunoassay (CMIA) with its dedicated kits (Abbott Diagnostics, Wiesbaden, Germany) and auto-analyzer (Abbott Architect I2000, IL, USA) were used to measure serum fasting plasma insulin (FPI) levels. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E_2), progesterone, DHEA-S, and total testosterone levels were also measured via CMIA (UniCel DXI 800, Beckman Coulter Inc., Brea, CA, USA). Additionally, the sex hormone-binding globulin (SHBG) level was measured via the chemiluminescence immunoassay technique (Immulite 2000 XPi, Simens Healthcare Diagnostics, Eschborn, Germany). The formula FAI: (total testosterone/SHBG)×100 was used to calculate FAI. Insulin resistance was measured via homeostasis model assessment of insulin resistance (HOMA-IR)[14] and quantitative insulin sensitivity check index (QUICKI)[15].

Measurement of circulating dermcidin by ELISA

Human enzyme-linked immunosorbent assay (ELISA) kits (Catalog number: 201-12-460, Sunred Bioscience, Shanghai, China) were used to measure dermcidin levels (in duplicate), following the instructions of manufacturer. Intra-assay coefficient of variability (CV) was <6% and the inter-assay CV was <8%. The level of circulation dermcidin range is between 1 and 300 ng/mL.

Statistical analysis

A power analysis using G Power 3.0.10 for Windows (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) was considered to obtain the scale of population in the current study. The number of subjects involved in each group was calculated using this program. Regarding the abovementioned program, a group of 70 subjects was selected for each group as α and study power values were 0.05 and 0.90, respectively.

A Statistical Package for the Social Sciences software version 18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The distribution of variables was checked using Kolmogorov-Smirnov in each group. Normally distributed data were displayed as mean with standard deviation (SD). Student's t-test was used for the comparison of variables. Pearson's correlation coefficients were used to reveal the correlation of neudesin with metabolic and hormonal parameters. A multiple regression analysis was used to show an independent link between neudesin and correlated parameters. The level of 95% for the confidence interval was used. A two-sided $p<0.05$ was considered statistically significant.

RESULTS

Clinical and laboratory characteristics of the study population

The demographic and laboratory results are given in Table 1. Circulating dermcidin levels were significantly increased in PCOS subjects compared to controls (172.53±42.41 vs. 108.44±31.69 ng/mL, $p<0.001$). HOMA-IR, insulin, and hs-CRP levels were significantly higher in women with PCOS, whereas QICKI levels were significantly lower in women with PCOS than controls. Blood pressures did not differ between groups. Triglycerides were notably elevated, whereas HDL-cholesterol levels were remarkably lower in PCOS subjects compared to control. Total cholesterol and LDL-cholesterol levels did not show significant differences.

Correlation and multivariate regression analysis

Dermcidin levels showed a positive correlation with BMI, hs-CRP, HOMA-IR, and BMI, whereas it displayed a negative

Table 1. Comparison of the demographic and laboratory characteristics of the subjects.

Variables	PCOS (n=75)	Controls (n=75)	p[a]
Age, years	30.46±6.85	29.89±6.73	0.608
BMI, kg/m^2	26.60±4.48	26.87±4.51	0.709
SBP, mmHg	108.97±12.80	107.46±11.77	0.451
DBP, mmHg	74.28±6.60	73.61±5.73	0.506
Ferriman-Gallwey score	14.60±2.86	4.25±1.19	<0.001*
FBG, mg/dl	83.88±8.18	81.67±5.86	0.060
Insulin, µIU/ml	17.27±6.20	10.83±4.44	<0.001*
HOMA-IR	3.60±1.41	2.18± 0.89	<0.001*
QUICKI	0.32±0.01	0.34±0.02	<0.001*
Total cholesterol, mg/dl	208.08±33.64	201.57±43.72	0.309
LDL-C, mg/dl	137.97±28.75	130.94±27.58	0.129
HDL-C, mg/dl	41.52±9.77	48.79±10.89	<0.001*
Triglycerides, mg/dl	142.95±33.07	109.18±29.72	<0.001*
hs-CRP, mg/l	1.22±0.54	0.67± 0.21	<0.001*
FSH, mIU/ml	6.86±1.82	7.25±1.89	0.202
LH, mIU/ml	14.07±4.20	8.56±3.01	<0.001*
Progesterone, ng/ml	1.10±0.23	1.16±0.25	0.149
Estradiol, pg/ml	50.67±12.05	49.06±8.11	0.339
Total testosterone, nmol/l	2.90±0.41	1.69±0.35	<0.001*
SHBG, nmol/l	37.56±11.66	68.38±14.95	<0.001*
FAI, %	8.19±1.73	2.48±0.12	<0.001*
DHEA-SO$_4$, µg/dl	184.77±72.53	152.50±39.34	0.001*
Dermcidin, ng/ml	172.53±42.41	108.44±31.69	<0.001*

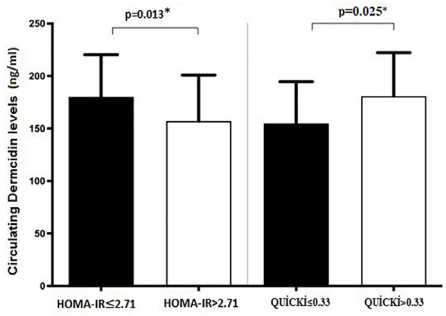
Results are given in mean±SD. [a]Independent samples Student's t-test was used. *A p<0.05 was considered significant. BMI: body mass index; DHEA-S: dehydroepiandrosterone sulfate; DBP: diastolic blood pressure; FAI: free androgen index; FBG: fasting blood glucose; FSH: follicle-stimulating hormone; HDL-C: high-density lipoprotein cholesterol; HOMA-IR: homeostasis model assessment of insulin resistance; hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; LH: luteinizing hormone; PCOS: polycystic ovary syndrome; QUICKI: quantitative insulin sensitivity check index; SBP: systolic blood pressure; SHBG: sex hormone-binding globulin.

correlation with QUICKI. Dermcidin levels exhibited a positive correlation with FBG, whereas dermcidin levels did not show a correlation with insulin levels. Moreover, dermcidin did not display any correlation with FSH, LH, estrogen, progesterone, and androgen as well as lipid profiles (Table 2). Dermcidin also showed an independent link with HOMA-IR and hs-CRP as well as an inversely independent link with QUICKI. Additionally, a positive correlation between dermcidin and BMI vanished in regression analysis (Table 2).

Comparing dermcidin levels in polycystic ovary syndrome subjects with and without insulin resistance using surrogate markers (quantitative insulin sensitivity check index and homeostasis model assessment of insulin resistance)

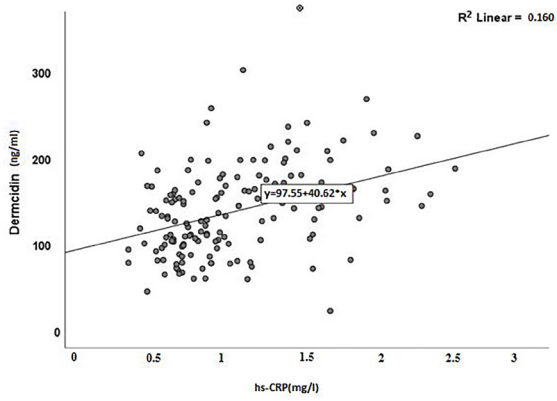
Polycystic ovary syndrome group was categorized into two different subdivisions according to the comprising insulin resistance (HOMA-IR>2.71 and HOMA-IR≤2.71 and QUICKI≤0.33 and QUICKI>0.33)[16,17]. Circulating dermcidin levels showed significant elevation in PCOS subjects having insulin resistance compared to those PCOS subjects not having insulin (Figure 2).

Since a statistically significant positive correlation was found between the dermcidin molecule and hs-CRP, mathematical modeling was performed to make an estimation according to the hs-CRP parameter by performing regression modeling, and the related equation is shown in Figure 3.



*Significance is defined as p<0.005.

Figure 2. Comparing dermcidin levels in PCOS.



*Significance is defined as p<0.005.

Figure 3. Predicting dermcidin with regression modeling according to hs-CRP.

Table 2. Pearson's correlation analysis and multiple regression analysis.

Variables	Correlation analysis		Multiple regression analysis			
	r	p	β	95%CI		p
				Lower	Upper	
Age	0.097	0.231	–	–	–	–
BMI	0.131	0.044*	0.053	-0.102	0.208	0.078
Insulin	0.098	0.064	–	–	–	–
FBG	0.287	0.012*	–	–	–	–
HOMA-IR	0.215	0.029*	0.214	0.091	0.337	0.019*
QUICKI	-0.197	0.034*	-0.159	-0.244	-0.074	0.038*
hs-CRP	0.162	0.041*	0.103	0.051	0.155	0.045*
FSH	0.045	0.267	–	–	–	–
LH	0.104	0.301	–	–	–	–
Estradiol	0.056	0.221	–	–	–	–
Progesterone	0.106	0.189	–	–	–	–
FAI	0.076	0.195	–	–	–	–
DHEA-S	0.085	0.206	–	–	–	–
Total cholesterol	0.112	0.087	–	–	–	–
LDL-C	0.058	0.228	–	–	–	–
HDL-C	-0.101	0.072	–	–	–	–
Triglycerides	0.109	0.065	–	–	–	–

Pearson's correlation analysis was used. *A $p<0.05$ was considered significant. Multiple linear regression analysis was used. β: unstandardized regression coefficient; CI: confidence interval; r: Pearson's correlation coefficient.

DISCUSSION

In the current study, we evaluated dermcidin levels in women with PCOS for the first time. We found that circulating dermcidin levels were significantly increased in PCOS subjects compared to controls. PCOS subjects with insulin resistance had higher levels of dermcidin than those PCOS subjects without insulin resistance. Dermcidin levels showed an independent link to HOMA-IR and hs-CRP, whereas dermcidin levels exhibited an inversely independent link to QUICKI.

Insulin resistance plays a key role in the pathophysiology of PCOS albeit the underlying cellular mechanisms are remaining unclear. In normal physiological conditions, insulin-stimulated glucose uptake mainly occurs through GLUT4 in muscle and fat tissues. It has been reported that GLUT4 protein expression is decreased in adipocytes of patients with PCOS[18]. Thus, the loss of GLUT4 in the adipocytes may be a significant contributor to the IR in patients with PCOS. Insulin receptor-mediated signal transduction is defective in women with PCOS as well[19]. Pre-clinical data suggest that dermcidin induces insulin resistance via inhibiting GLUT4 gene expression and subsequently dermcidin impairs glucose uptake in cells[6]. In the current study, we found that dermcidin levels were notably elevated in PCOS subjects. Consistently, we found that insulin resistance marker-HOMA-IR levels were increased, whereas insulin sensitivity marker-QUICKI levels were reduced in PCOS women. Moreover, we determined that dermcidin levels showed exhibited an independent link with HOMA-IR, whereas dermcidin displayed an inversely independent link with QUICKI. Additionally, PCOS subjects with insulin resistance had higher levels of dermcidin than those PCOS subjects without insulin resistance. In light of these data, dermcidin may play a role in the development of insulin resistance in PCOS subjects. Pre-clinical data suggest that dermcidin inhibits insulin secretion albeit we could not find any relation between dermcidin and insulin levels.

Polycystic ovary syndrome (PCOS) is associated with chronic low-grade inflammation. It has been reported that a variety of inflammatory markers in women with PCOS including CRP, tumor necrosis factor-α, and interleukin 6 are increased[1,2,20]. The etiology of systemic inflammation in PCOS remains unclear. Dermcidin plays a crucial role in

host immune defense. It has been reported that dermcidin induced TNF-α synthesis in liver cells[6]. In the current study, we found that circulating hs-CRP levels were higher in subjects with PCOS compared to controls. Moreover, we determined an independent link between dermcidin and hs-CRP. These data suggest that increased dermcidin may play a role in the development of inflammation in PCOS subjects.

Few clinical studies are currently involved in investigating the dermcidin levels; however, no data have yet been obtained regarding the relationship between dermcidin and metabolic parameters. A study showed that dermcidin plays a crucial role in the pathogenesis of T1DM as well as in the severity of the disease[6]. It was reported that dermcidin induced insulin resistance via inhibiting glucose uptake in the liver by decreasing GLUT4 synthesis. In addition, dermcidin induced inflammation[7,8]. In another study, circulating dermcidin levels in milk were notably elevated in subjects with gestational diabetes compared to controls[9].

We had some limitations in our study. Insulin resistance was evaluated using formulations instead of the insulin clamp technique, a gold standard but invasive method. Although this cross-sectional designed study does not provide causality, it allows discovering the link between molecules and disorders.

In conclusion, increased dermcidin levels were independently related to the degree of insulin resistance and inflammation in women with PCOS. Dermcidin may play a role in developing insulin resistance and inflammation in PCOS, which needs further research.

COMPLIANCE WITH ETHICAL STANDARDS

The subjects gave their oral and written informed consent before their inclusion in the study. The study adhered strictly to the principles of the Declaration of Helsinki as revised in 2008.

AUTHORS' CONTRIBUTIONS

OYA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software. **OB:** Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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