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Original Article

Peroxiredoxin 4 levels in patients with PCOS and/or obesity

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ABSTRACT

Background: Peroxiredoxin 4 is a part of endogen antioxidant system and its levels are elevated in increased oxidative stress conditions. It is found to be positively associated with cardiovascular risk. The aim of the study was to investigate peroxiredoxin 4 levels in women with polycystic ovarian syndrome (PCOS) and/or obesity.
Methods: In this cros-sesctional study were included 80 patients. Anthropometric measurements and biochemical tests, including peroxiredoxin 4 measurement, were performed.
Results: There was a tendency towards lower peroxiredoxin 4 levels in non-obese PCOS subjects (5674.8 ± 3822.4 pg/ml), higher in obese PCOS (6588.9 ± 3731.0 pg/ml) and even higher in obese patients without PCOS (7724.6 ± 4840.4 pg/ml). Patients with abdominal obesity according to waist circumference and waist-to-hip ratio had significantly higher levels of peroxiredoxin compared to those without (7108.2 ± 4568.0 vs. 5079.8 ± 2555.4 pg/ml; $p = 0.015$ and 7310.6 ± 2646.2 vs. 4785.0 ± 2646.2 pg/ml; $p = 0.013$). There was no difference in peroxiredoxin 4 levels in patients with and without insulin resistance, hypertension, dislipidemia, hyperandrogenemia, metabolic syndrome. Peroxiredoxin 4 showed weak positive correlation to weight ($r = 0.228$; $p = 0.044$) and visceral adiposity index ($r = 0.278$; $p = 0.031$) and higher to erythrocyte sedimentation rate ($r = 0.4$; $p < 0.01$), but not to hormonal parameters and insulin sensitivity indexes.
Conclusions: Non-obese patients with PCOS have a tendency towards lower peroxiredoxin 4 levels compared to obese patients with and without PCOS. Patients with abdominal obesity have significantly higher peroxiredoxin 4 levels than those without. We were not able to prove correlation between peroxiredoxin 4 levels and hormonal and carbohydrate status of the PCOS patients.

Introduction

PCOS is a common disorder that affects approximately 6–10% of women of reproductive age [1,2] and is a major cause of menstrual disturbances, hirsutism and female anovulatory infertility. According to some studies PCOS patients have an adverse cardiovascular risk profile - increased risk for diabetes mellitus [3,4], arterial hypertension [5], dislipidemia [6–8] and subclinical inflammation and atherosclerosis [9–11]. Cardiovascular risk factors are usually present even in younger age and this suggests that the chronic disturbances in hormonal and metabolic status typical for the syndrome predispose the patients to development of early atherosclerosis and premature clinical presentation of cardiovascular disease.

Atherosclerosis is a state of oxidative stress with increased production of reactive oxygen species (ROS) by endothelial, vascular smooth muscle, and adventitial cells [12]. There are several systems in the organism that react against oxidative stress and thus protect form vascular damage [13]. One such system are the peroxiredoxins. They act as a powerful protective mechanism that keeps the balance between oxidants and antioxidants in normal conditions and in oxidative stress. Peroxiredoxins are thiol-dependent peroxidases that degrade the endogenous peroxides [14–16]. In increased oxidative stress conditions there is an overexpression of those enzymes [17,18]. Some studies demonstrate that the increased levels of peroxiredoxin 4 are linked to higher risk of cardiovascular diseases and increased cardiovascular mortality [19]. Moreover, elevated serum peroxiredoxin 4 levels are associated with a higher risk of incident type 2 diabetes [20].

There are no studies focused on plasma peroxiredoxin 4 levels in patients with PCOS and their link to cardiovascular risk factors.

The **aim** of the present study was to investigate peroxiredoxin 4 levels in women with PCOS and/or obesity.

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Patients and methods

In the present study were included patients with PCOS and/or obesity hospitalizaed in endocrine clinic of University hospital that met the following inclusion and exclusion criteria.

Inclusion criteria

- premenopausal women aged 18 to 45
- PCOS, diagnosed by European Society of Human Reproduction and Embryology - American Society for Reproductive Medicine (ESHRE-ASRM) criteria [21] OR
- obesity (BMI > 30 kg/m^2)

Exclusion criteria

- Pregnancy
- Serious illnesses as cardiac, renal or liver insufficiency
- Other endocrine pathology like type 2 diabetes mellitus, adrenal tumors/hyperplasia, hypothyroidism, pituitary tumors, hypogonadism.
- Insulin sensitizing medication (metformin or glitazones) or combined oral contraceptive (COC) use less than 4 months prior to the study

The study was performed in adherence with the guidelines of the Declaration of Helsinki and was approved by the local ethics committee. All the patients signed an informed consent for participation in the study.

Patients were divided into three groups – *Obese* (group 1), *Non-obese PCOS (BMI < 30 kg/m2)* (group 2) and *Obese PCOS* (group 3).

The following information for each patient was obtained:

General information – name, age;

Anthropometric data – height, weight, body mass index (BMI), waist circumference, hip circumference, waist-to-hip ratio (WHR), waist-to-stature ratio (WSR); All measurements were performed in a standing position with feet together, relaxed abdomen and arms at their sides. Waist circumference of subjects was measured by placing a soft tape measure midway between the lowest rib and the iliac crest and hip circumference at the level of the great trochanters. All the measurements were performed after overnight fasting. Patients were considered to have abdominal obestity if they had waist circumference > 80 cm and/or WHR > 0.85 and/or WSR > 0.5.

Obesity was diagnosed at BMI ≥ 30 kg/m2;

Polycystic ovary syndrome was diagnosed according to the ESHRE-ASRM criteria– two out of the following: 1) oligo/amenorrhea; 2) clinical or biochemical hyperandrogenism and 3) polycystic ovaries at ultrasound examination when all other endocrine causes are excluded;

Oral glucose tolerance test (OGTT) – blood glucose (BG) and imunoreactive insulin (IRI) measured on 0, 60 and 120 min;

Hormones (testosterone, androstendione, dehydroepiandrosteron sulphate (DHEAS), 17-OH-progesterone, estradiol, LH, FSH, TSH, prolactin); For measuring testosterone an electrochemiluminiscence (ECLIA) method was used by analytics Elecsys 2010 (analytical sensitivity 0.069 nmol/l (0.02 ng/ml). For measuring DHEAS an electrochemiluminiscence (ECLIA) method was used by analytics Elecsys 2010 (sensitivity 0.003 mcmol/l). Androstendione was measured by solid phase enzyme-linked immunosorbent assay (ELISA), based on the principle of competitive binding (analytical sensitivity 0.019 ng/ml (0.663 nmol/l)). 17-OH-progesterone was measured by solid phase enzyme-linked immunosorbent assay (ELISA), based on the principle of competitive binding (analytical sensitivity 0.034 ng/ml (0.103 nmol/l)). Estradiol was measured by an immunochemiluminiscent test (analytical sensitivity 7.9 pg/ml (29 pmol/l)). LH was measured by an immunochemiluminiscent test (analytical sensitivity 0.07 IU/l). FSH was measured by an immunochemiluminiscent test (analytical sensitivity 0.03 IU/l). All the laboratory tests were performed in the Central Clinical Laboratory of the Alexandrovska University Hospital in Sofia, which is the reference laboratory for the country

Peroxiredoxin 4 levels were measured by an enzyme-linked immunosorbent assay. Blood samples for Preoxiredoxin 4 analysis were taken after overnight fast on days 2–5 of a spontaneous or progestin-induced menstrual cycle, and the serum was separated and frozen;

Metabolic syndrome (MetS) was diagnosed according to the International Diabetes Federation (IDF) and American Heart Association and the National Heart, Lung, and. Blood Institute (AHA/NHLBI) criteria – 3 out of 5 risk factors – increased waist circumference (>80 cm), increased TG (>1.7 mmol/l), decreased HDL (<1.3 mmol/l), increased BP (>130/85 mmHg) and increased fasting blood glucose (>5.5 mmol/l), or present treatment for these disturbances [25]. Arterial hypertension was diagnosed if there was such a diagnosis in the patient's file and/or there was antihypertensive treatment and/or a measurement during the hospital stay of arterial blood pressure (BP) 140/90 mmHg. and type of antihypertensive medications were also recorded. Blood pressure was measured on the right arm, with the subjects in a sitting position and relaxed.

Statistical methods

The data were processed using the statistical package SPSS 16.0. The level of significance for rejecting the null hypothesis was $p < 0.05$. Data are presented as mean ± SD.The following statistical methods were applied: descriptive analysis, variation analysis, Kolmogorov–Smirnov's one sample non-parametric test, Kruskal-Wallis non-parametric test, one-way analysis of variance between-groups ANOVA, and correlation analysis. Nonparametric Kolmogorov-Smirnov and Shapiro-Wilk tests were used for the determination of distribution. For variables without normal distribution logarithmic transformation was apllied. If there still was no normal distribution, nonparametric methods were used. Difference between the 3 groups was analyzed using single-factor dispersion analysis ANOVA (normal distribution) or Kruskal-Wallis (not normal distribution) tests.

Results

In the present study we included 80 patients – 25 *Obese*, 35 *Non-obese PCOS* and 20 *Obese PCOS* women. Anthropometric characteristics of the three groups are shown on Table 1.

The markers of carbohydrate metabolism are sown on Table 2. The data about lipid profile and arterial blood pressure are shown on Table 3.

The groups were similar in age but non-obese PCOS patients had significantly lower BMI, waist circumference, WHR and WSR than obese and obese PCOS subjects.

There was a tendency towards lower peroxiredoxin 4 levels in non-obese PCOS subjects (5674.8 ± 3822.4 pg/ml), higher in obese PCOS (6588.9 ± 3731.0 pg/ml) and even higher in obese patients without PCOS (7724.6 ± 4840.4 pg/ml) (Fig. 1).

To investigate whether obesity per se or abdominal adiposity are more important for the differences in peroxiredoxin 4 levels in nonobese and obese subjects we divided all the patients based on the presence or absence of abdominal obesity. The data about the presence of visceral obesty according to the different criteria are presented on table. Patients with abdominal obesity according to waist circumference and WSR had significantly higher levels of peroxiredoxin compared to those without (7108.2 ± 4568.0 vs. 5079.8 ± 2555.4 pg/ml; $p = 0.015$ and 7310.6 ± 2646.2 vs. 4785.0 ± 2646.2 pg/ml; $p = 0.013$) (Fig. 2).

Table 1
Anthropometric characteristics of the groups.

	Group 1 Obese (n = 25)	**Group 2** Non-obese PCOS (n = 35)	**Group 3** Obese PCOS (n = 20)
Age(years)	28.5 ± 5.7	26.0 ± 4.7	25.1 ± 4.8
BMI (kg/m^2)	39.9 ± 8.8$^{\wedge\wedge\wedge}$	22.9 ± 3.3***	36.2 ± 6.1
Waist (cm)	111.4 ± 13.1$^{\wedge\wedge\wedge}$	78.1 ± 9.7***	104.4 ± 13.5
WHR	0.89 ± 0.09$^{\wedge\wedge\wedge}$	0.79 ± 0.06***	0.88 ± 0.09
WSR	0.68 ± 0.09$^{\wedge\wedge\wedge}$	0.47 ± 0.06***	0.64 ± 0.09

*** p<0,001 between group 2 and group 3.
$^{\wedge\wedge\wedge}$ p<0,001 between group 1and group 2.

Table 2
Carbohydrate metabolism markers of the groups.

	Group 1 Obese (n = 25)	**Group 2** Non-obese PCOS (n = 35)	**Group 3** Obese PCOS (n = 20)
Blood glucose 0 min (mmol/l)	4.3 ± 0.7	4.1 ± 0.6	4.6 ± 1.1
Blood glucose 60 min (mmol/l)	7.2 ± 1.8	6.9 ± 1.9	7.8 ± 1.9
Blood glucose 120 min (mmol/l)	5.9 ± 1.5	5.7 ± 1.3	6.0 ± 1.6
IRI 0 min (mmol/l)	17.8 ± 10.9	8.4 ± 4.0$^{\wedge\wedge\wedge}$	22.6 ± 11.8***
IRI 60 min (mmol/l)	107.6 ± 99.5	71.2 ± 60.0	137.1 ± 74.1*
IRI 120 min (mmol/l)	58.5 ± 47.6	41.2 ± 32.7	68.9 ± 54.1
HOMA index	3.5 ± 2.1	1.5 ± 0.7$^{\wedge\wedge}$	4.8 ± 3.6***
Insulin resistance prevalence (%)	60%	28.6%$^{\wedge\wedge\wedge}$	80%***
Prevalence of prediabetes (%)	16%	5.7%	10%

* p<0,05 between group 2 and group 3.
*** p<0,001 between group 2 and group 3.
$^{\wedge\wedge}$ p<0,01 between group 1 and group 2.
$^{\wedge\wedge\wedge}$ p<0,001 between group 1and group 2.

Table 3
Lipid metabolism and blood pressure between groups.

	Group 1 Obese (n = 25)	**Group 2** Non-obese PCOS (n = 35)	**Group 3** Obese PCOS (n = 20)
Dislipidemia (%)	60%	24.2%$^{\wedge}$	47.4%*
Total cholesterol (mmol/l)	4.6 ± 0.7	4.6 ± 0.7	4.6 ± 0.8
HDL (mmol/l)	1.2 ± 0.3	1.6 ± 0.4$^{\wedge\wedge\wedge}$	1.4 ± 0.3
LDL (mmol/l)	2.7 ± 0.7	2.7 ± 0.5	2.6 ± 0.6
VLDL (mmol/l)	0.6 ± 0.4	0.4 ± 0.2$^{\wedge}$	0.6 ± 0.3
Triglicerides (mmol/l)	1.5 ± 0.9	0.9 ± 0.4$^{\wedge\wedge}$	1.4 ± 0.6**
Arterial hypertension (%)	20%	2.9%	16%
Systolic BP (mmHg)	119.4 ± 9.6	115.1 ± 10.7	120.5 ± 17.3
Diastolic BP (mmHg)	77.4 ± 8.6	71.7 ± 7.5^	75.0 ± 11.0

*p<0,05 between group 2 and group 3.
**p<0,01 between group 2 and group 3.
***p<0,001 between group 2 and group 3.
$^{\wedge}$p<0,05 between group 1 and group 2.
$^{\wedge\wedge}$p<0,01 between group 1 and group 2.
$^{\wedge\wedge\wedge}$p<0,001 between group 1and group 2.

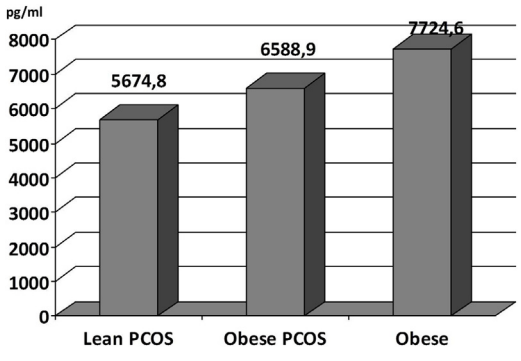

Fig. 1. Peroxiredoxin levels in non-obese PCOS, obese PCOS and obese patients without PCOS.

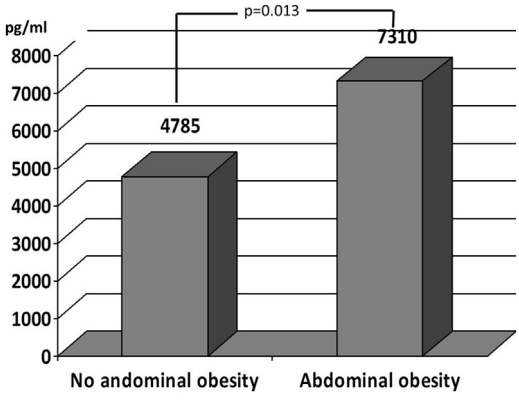

Fig. 2. Peroxiredoxin levels in patients with and without abdominal obesity.

Table 4
Viscera obesity according to different criteria.

	Group 1 Obese (n = 25)	**Group 2** Non-obese PCOS (n = 35)	**Group 3** Obese PCOS (n = 20)
WC>80 cm	100%***	37.1%	100%
WHR > 0,85	80%***	15.4%	83.3%
WSR > 0,5	100%***	34.3%	95%

*** p<0,001.

There was no difference in peroxiredoxin 4 levels in patients with and without insulin resistance, hypertention, dyslipidemia, hyperandrogenemia, metabolic syndrome. Peroxiredoxin showed weak positive correlation to weight ($r = 0.228$; $p = 0.044$) and VAI ($r = 0.278$; $p = 0.031$) and higher to erythrocyte sedimentation rate ($r = 0.4$; $p < 0.01$), but not to hormonal parameters and insulin sensitivity indexes. The prevalence of abdominal obesity in the three groups is shown in Table 4.

Discussion

Polycystic ovarian syndrome is a condition that predisposes affected women to higher risk of cardiovascular diseases and carbohydrate disturbances. On the other hand the high prevalence of obesity is an additional risk factor. Many studies demonstrate elevated oxidative stress in PCOS patients. A meta-analysis by Murri et al [22]. shows that homocysteine concentrations were increased by 23%, malondialdehyde levels by 47%, asymmetric dimethylarginine levels by 36%, superoxide dismutase activity was 34% higher in women with PCOS compared with controls. The mean glutathione levels were 50% lower and mean paraoxonase-1 activity was 32% lower in women with PCOS compared with controls.

Peroxiredoxin 4 is a part of endogenous antioxidant system and its levels are not only increased in oxidative stress conditions, but also are linked to the risk of cardiovascular morbidity and mortalty In the present study the levels of peroxiredoxin 4 were higher in obese patients with and without PCOS than in non-obese PCOS subjects although without reaching statistical significance, but were significantly higher in patients with abdominal obesity than those without and there was a weak positive correlation to weight. This means that obesity and especially abdominal adiposity is the main factor for peroxiredoxin 4 elevation in this population of patients. In a study by González et al. obese PCOS and non-PCOS patients had higher p47phox, that plays a role in superoxide radical production, than lean PCOS and non-PCOS women [23], supporting the hypothesis that obesity may influence ROS-induced oxidative stress in obese PCOS women.

Because of the low prevalence of prediabetes we could not confirm the role of glycemic disturbances for peroxiredoxin 4 levels. Again, there was no difference between patients with and without insulin resistance. Peroxiredoxin 4 levels were independent of hormonal status and menstrual disturbances in PCOS patients. Other studies suggest that PCOS is an independent factor for increased oxidative stress [24]. In our study, however, nonobese PCOS subjects had the lowest levels of peroxiredoxin 4. A limitation of our study is the lack of lean control group.

This is the first study that demonstrates the role of abdominal obesity for elevated peroxiredoxin 4 levels in patients with PCOS and obesity.

Conclusions

1 Non-obese patients with PCOS have a tendency towards lower peroxiredoxin 4 levels compared to obese patients with and without PCOS
2 Patients with abdominal obesity have significantly higher peroxiredoxin 4 levels than those without
3 We were not able to prove correlation between peroxiredoxin 4 levels and hormonal and carbohydrate status of the PCOS patients

Disclosure

The authors declare no conflict of interest.

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Contribution to authorship

AG and ZK designed and conducted the study and performed statistical analysis. TV performed the laboratory tests.

Details of ethics approval

The study was performed in adherence with the guidelines of the Declaration of Helsinki and was approved by the local ethics committee. All the patients signed an informed consent for participation in the study. The study was approved by The Ethics Committee for Science Studies of Medica Unievrsity Sofia, Protocol number 2/14.04.2016.

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