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Myeloperoxidase Levels in Patients with PCOS and/or Obesity Before and After Metformin Treatment

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Abstract

Objectives: Polycystic Ovarian Syndrome (PCOS) is often linked to adverse cardiometabolic profile. Myeloperoxidase (MPO) is an enzyme, secreted from white blood cells that generates Radical Oxygen Species (ROS) and is thought to be involved in increased Cardiovascular (CV) risk. The aim of the present study is to compare MPO in premenopausal patients with PCOS with and without obesity (+/- obesity) to other classical cardiovascular risk factors before and after metformin treatment.

Materials and Methods: In this study 75 women including 27 obese, 31 lean PCOS and 17 obese PCOS patients participated. Anthropometric measurements and biochemical study including MPO measurement were performed in the beginning of the study. Patients that had insulin resistance were treated with 1500-3000 mg metformin and all the tests were repeated after mean 6.8 months.

Results: MPO levels were similar between patients with obesity only and obesity with PCOS and in patients with PCOS only and obese PCOS patients. We found no differences in MPO levels between patients with different PCOS phenotype, with and without visceral obesity or insulin resistance based on variety of criteria, with and without arterial hypertension, dyslipidemia, menstrual disturbances and obstructive sleep apnea. There was no significant change in MPO levels after several months of metformin treatment, despite the beneficial changes in insulin concentrations and erythrocyte sedimentation rate.

Conclusion: MPO levels were similar between patients with obesity +/- PCOS, and in patients with PCOS +/- obesity. MPO did not change significantly after metformin treatment.

Keywords: Polycystic Ovarian Syndrome, Peroxidase, Inflammation

Introduction

Polycystic Ovarian Syndrome (PCOS) affects 6-10% of premenopausal women and causes menstrual disturbances, hirsutism and female anovulatory infertility (1,2). There are studies that show increased diabetes risk and higher rate of arterial hypertension (3-6), dyslipidemia and atherosclerosis in PCOS patients (6-12). As Cardiovascular (CV) risk factors are present at a younger age, characteristic features of the syndrome can lead to earlier atherosclerosis and premature Cardiovascular Diseases (CVD).

Inflammation is a feature of atherosclerosis. Myeloperoxidase (MPO) is an enzyme, secreted form white blood cells that generates Radical Oxygen Species (ROS). It is probably involved in increased CV risk.

MPO reduces Nitric Oxide (NO) bioavailability and impairs vasodilation (13). MPO is higher in obese patients than in control subjects (14). PCOS patients with insulin resistance have higher MPO levels than patients without insulin resistance (15). PCOS can cause inflammation due to elevated MPO independently of hormone levels, BMI and other risk factors (16).

There are no data on the effect of metformin on MPO in PCOS patients. The aim of the present study is to compare MPO in premenopausal patients with PCOS with and without obesity (+/- obesity) to other classical CV risk factors before and after metformin treatment.

Materials and Methods

In this study 75 women including 27 obese, 31 lean PCOS and 17 obese PCOS patients participated. The inclusion and exclusion criteria were as follows:

Inclusion criteria

- obesity (BMI > 30 kg/m^2)
- PCOS, diagnosed by ESHRE-ASRM criteria (17)
- premenopausal women aged 18 to 45 yr

Exclusion criteria

- Pregnancy
- Serious illnesses as cardiac, renal or liver insufficiency
- Other endocrine pathologies such as type 2 diabetes mellitus, pituitary tumors, adrenal tumors, hypogonadism, hypothyroidism,
- Insulin sensitizing medication (metformin or glitazones) or Combined Oral Contraceptive (COC) use less than 4 months prior to the study.

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Patients were divided into three groups: obese (group 1), lean PCOS (group 2) and obese PCOS (group 3).
We obtained the following information on every patient:
1. *Anthropometric data:* height, weight, Body Mass Index (BMI), waist circumference, hip circumference, Waist-to-Hip Ratio (WHR), Waist-to-Stature ratio (WSR).
2. *Presence of obesity:* BMI≥ 30 kg/m^2 (18).
3. *PCOS* was diagnosed according to the ESHRE-ASRM criteria i.e. two out of the following: 1) oligo/amenorrhea; 2) clinical or biochemical hyperandrogenism and 3) polycystic ovaries on ultrasound examination when all other endocrine causes are excluded.
4. *Presence of arterial hypertension:* BP ≥ 140/90 mmHg or drugs for Arterial Hypertension (AP) (19).
5. *Lipid profile:* Total Cholesterol (TC), HDL-cholesterol (HDL), LDL-cholesterol (LDL), VLDL-cholesterol, Triglycerides (TG).
6. *Oral Glucose Tolerance Test* (OGTT)
7. *MPO* levels
The patients that were diagnosed with insulin resistance based on fasting Immunoreactive Insulin (IRI) (≥20 mU/l), IRI on 120 min (≥100 mU/l) or HOMA index (>2.0) started metformin treatment (1500-3000 mg/day) and were re-evaluated after mean 6.8 months and all the laboratory test and anthropometric measurements were repeated.

Measurement of serum MPO levels
Blood for MPO was taken after overnight fast and the serum was frozen. MPO levels were measured by an enzyme-linked immunosorbent method.

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. The following statistical methods were applied: descriptive analysis, tests for normality of distribution (Kolmogorov–Smirnov's one sample test), Student's t-test for two independent samples, Mann–Whitney's non-parametric test for two independent samples (for variables that do not have normal distribution), One-way analysis of variance between-groups ANOVA, and correlation analysis. Data are presented as mean±SD.

Results
In the present study we included 75 patients including: Group 1 (27 obese), Group 2 (31 lean PCOS) and Group 3 (17 obese PCOS women) (Table 1). The MPO levels were similar between the three groups (Table 2). A large number of patients however had MPO levels above the upper limit.
MPO levels in PCOS patients were independent of PCOS phenotype, presence of visceral obesity or insulin resistance, arterial hypertension, dyslipidemia, menstrual disturbances, hyperandrogenemia and obstructive sleep apnea. MPO levels correlated positively with serum creatinine levels (r=0.348, P= 0.004) and MCHC (r=0.405, P= 0.001).
Of the 75 patients included in the study, insulin resistance was diagnosed in 40 (53.3%) and metformin treatment was started. Two of them became pregnant, 15 stopped their treatment because of side effects or were lost for follow-up and 23 came back for re-evaluation. The data before and after metformin treatment are shown in Table 3.
After mean 6.8 months of metformin treatment we found a reduction in mean weight and BMI which was not statistically significant. Significant reduction was observed in IRI levels on 0 and 60 min, HOMA and ESR. Serum concentrations of MPO did not significantly change before and after metformin treatment (P= 0.082), although there was tendency towards lower levels. There was no correlation between the change of MPO levels and body weight after the treatment (r=0.058, P= 0.84) and we found no difference in MPO levels in patients who did or did not restore normal menstrual cycle after metformin use (P= 0.83).

Discussion
Some studies demonstrate that premenopausal women with PCOS show an adverse cardiometabolic profile

Table 1. Anthropometric characteristics of the groups

	Group 1 Obese (n=27)	Group 2 Lean PCOS (n=31)	Group 3 Obese PCOS (n=17)
Age(years)	29.3±6.3	26.8±4.5	26.2±4.3
BMI (kg/m^2)	40.0±8.6**	22.9±3.4***	35.9±6.6*
Waist (cm)	111.4±12.9**	79.2±9.6***	104.5±14.4
Hip (cm)	124.8±11.2**	98.2±9.9***	117.5±9.5*
WHR	0.89±0.09**	0.80±0.06***	0.89±0.08
WSR	0.68±0.09**	0.48±0.06***	0.64±0.09

PCOS= Polycystic ovarian syndrome; BMI= Body mass index; WHR= Waist to hip ratio; WSR= Waist to stature ratio.
*P<0.05 between group 1 and group 3; **P<0.001 between group 1and group 2; ***P<0.001 between group 2 and group 3.

Table 2. MPO-1 levels

	Group 1 Obese	Group 2 Lean PCOS	Group 3 Obese PCOS
MPO pg/ml	162.3±103.0	234.6±205.8	170.0±155.9
MPO> upper limit (72.67 ng/ml)	85.2%	87.1%	82.4%

PCOS= Polycystic ovarian syndrome; MPO= Myeloperoxidase

Table 3. Results before and after metformin treatment

	Before treatment	After treatment
Body weight (kg)	82.9±20.6	81.5±21.3
BMI (kg/m^2)	31.7±7.7	31.2±7.8
IRI OGTT 0 min (mU/l)	18.2±9.8	12.3±6.9**
IRI OGTT 60 min (mU/l)	133.1±84.8	105.5±72.7*
IRI OGTT 120 min (mU/l)	92.4±59.2	79.0±63.4
HOMA index	3.5±1.9	2.4±1.4*
ESR	17.6±10.8	8.7±5.6***
MPO pg/ml	262.3±248.6	152.0±113.3

BMI= Body mass index; IRI= Imunoreactive insulin; OGTT= Oral glucose tolerance test; HOMA= Homeostatsis model assessment; ESR= Erythrocyte sedimentation rate
*P<0,05; **P<0,01; ***P<0,001

(5,6,20). Finding new markers of increased cardiovascular risk in these patients could be very useful for early risk assessment and primary prevention. Oxidative stress participates in the progression of atherosclerosis. Studies show the role of MPO for oxidative modification of lipoproteins in the artery wall (21). Serum MPO levels are higher in PCOS patients than in healthy controls (16). Most of the patients in our study had MPO levels above the upper limit. There was no difference in MPO levels between patients with obesity +/- PCOS and in patients with PCOS +/- obesity.

A limitation of our study is the fact that we did not have a healthy control group. We did not find a link between MPO levels and the studied classical factors for CV risk.

Metformin treatment did not improve MPO levels despite the beneficial changes in insulin sensitivity and the decrease in erythrocyte sedimentation rate.

Conclusion

1. MPO levels were similar between patients with obesity +/- PCOS, and in patients with PCOS +/- obesity.
2. MPO did not change significantly after metformin treatment.

Ethical issues

The study was carried out in accordance to the code of ethics of the Declaration of Helsinki. All the patients signed an informed consent for participation in the study.

Conflict of interests

The authors declare no conflict of interests.

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