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Short Communication

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Serum Uric Acid Concentration in Overweight and Obese Women with Polycystic Ovary Syndrome

Nivelul acidului uric la femeile supraponderale și obeze cu sindromul ovarelor polichistice

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Abstract

***Background**: Women with polycystic ovary syndrome (PCOS) are at high risk for the development of diabetes mellitus, hypertension and coronary heart disease. Due to the inverse correlation between serum uric acid and insulin sensitivity, the measurement of uric acid may provide a marker of insulin resistance. **Objective**: To establish the relationship between uric acid and markers of insulin resistance in obese and overweight women with PCOS. **Methods**: Serum uric acid levels were measured in 38 PCOS obese and overweight patients and 30 controls matched for age and body mass index (BMI). Anthropometric variables, plasma glucose and insulin levels were measured. Insulin resistance was evaluated by homeostasis model assessment (HOMA-IR). **Results**: No statistically significant differences in uric acid levels between PCOS and non-PCOS women were found. Serum uric acid levels were positively correlated with BMI, waist circumference, insulin and HOMA. Following the use of stepwise linear regression analysis, BMI was the only parameter retained by the regression model, responsible for 42.1% of the variability of serum uric acid levels. **Conclusions**: In PCOS women obesity seems to be the main determinant of plasma uric acid levels. Insulin and HOMA are also involved to a lesser extent, but their role remains to be clarified by further studies.*

***Keywords**: PCOS, uric acid, obesity, insulin, HOMA-IR*

Rezumat

*Femeile cu sindromul ovarelor polichistice (PCOS) au un risc crescut de a dezvolta diabet zaharat, hipertensiune arterială și afectare coronariană. Datorită corelației negative dintre nivelul seric al acidului uric și sensibilitatea la insulină, determinarea acidului uric ar putea reprezenta un marker al rezistenței la insulină. **Obiectiv**: Stabilirea relației dintre acidul uric și markeri ai rezistenței la insulină la femeile supraponderale și obeze cu PCOS. **Metodă**: Nivelul seric al acidului uric a fost măsurat la un lot de 38 de paciente supraponderale și obeze cu PCOS comparativ cu un lot control alcătuit din 30 de femei cu aceeași vârstă și indice de masă corporală*

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(BMI). Au fost evaluați parametri antropometrici, nivelul glicemiei și insulinemiei. Rezistența la insulină a fost apreciată prin calcularea indicelui HOMA (HOmeostasis Model Assessment). ***Rezultate****: Nu au existat diferențe statistic semnificative între nivelurile de acid uric la femeile cu PCOS comparativ cu femeile fără PCOS. Nivelul acidului uric s-a corelat pozitiv cu BMI, circumferința taliei, insulină și HOMA. Aplicând analiza regresiei liniare, am observat că BMI a fost singurul parametru responsabil de 42,1% din variabilitatea nivelului acidului uric.* ***Concluzii****: La femeile cu PCOS obezitatea pare principalul determinat al nivelului de acid uric. Insulina și HOMA sunt implicate de asemenea în mai mică măsură, rolul lor urmând a fi clarificat în studii viitoare.*

Cuvinte cheie*: PCOS, acid uric, obezitate, insulină, HOMA-IR*

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Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in premenopausal women, with a prevalence of 5%-7% (1-3). The clinical and biochemical profile is heterogeneous, but anovulation, infertility and hirsutism represent the classical features (4, 5). The consequences of PCOS extend beyond the reproductive axis. The syndrome is associated with metabolic disturbances and cardiovascular risk factors such as obesity, insulin resistance and hyperinsulinemia, type 2 diabetes mellitus, dyslipidemia, and endothelial dysfunction. Thus, PCOS can be considered a variant of the metabolic syndrome (6).

To date, a number of classic and non-classic markers of cardiovascular risk have been identified in PCOS, uric acid being one of them.

Studies have shown that uric acid has inflammatory, proliferative and oxidative actions at endothelial level, thus increasing the cardiovascular risk (7, 8). Moreover, an inverse correlation between uric acid levels and insulin sensitivity in patients with metabolic syndrome has been reported. Thus, hyperuricemia was considered an inherent feature of the metabolic syndrome (9).

Taking into account these data, uric acid may be used as a simple diagnostic marker to identify the risk for metabolic syndrome and insulin resistance. The significance of uric acid level as a marker and/or risk factor for metabolic syndrome in PCOS is still controversial, and further aspects remain to be studied (10-12).

The aim of the present study was to evaluate the relationship between uric acid and markers of insulin resistance in obese and overweight women with PCOS.

Material and methods

The present study is part of a more ample project dealing with the metabolic and cardiovascular risk markers in PCOS.

The study group included 38 overweight (BMI between 25-29.9 kg/m^2) and obese (BMI $\geq$ 30 kg/m^2) women with PCOS. The diagnosis of PCOS was made using the ESHRE/ASMR Rotterdam criteria (clinical and/or biochemical hyperandrogenism, chronic anovulation, and polycystic ovaries on ultrasound) (13). Thirty age- and weight- matched women without PCOS served as controls.

The criteria for inclusion in the study group were: confirmed diagnosis of PCOS, overweight or obesity, and age 18-40 years. For the control group, the inclusion criteria were history of regular menses (26-32 days), overweight or obesity, and absence of other androgen excess disorders, PCOS included.

Exclusion criteria for both groups were previous diagnosis of hypertension or diabetes mellitus, chronic inflammatory diseases, acute illnesses, use of insulin sensitizing agents, oral contraceptive pills or other antiandrogen agents in the last 6 months, treatment with corticosteroids and other anti-inflammatory drugs, and age over 40 years. Women over 40 years of age were excluded due to the risk of confusing the

perimenopausal menstrual disturbances with oligo-amenorrhea in PCOS.

Blood samples were collected at 08.00 a.m. following overnight fast, during the early follicular phase (days 3-5) of control women and PCOS women presenting normal menses or bradymenorrhea, or at random for PCOS women with oligo-amenorrhea. The sera were stored at -20º C until analyzed.

A written informed consent was obtained from all patients and controls after getting the ethical review board approval.

Assays

Serum gonadotropins (FSH – follicle stimulating hormone and LH – luteinizing hormone) and testosterone levels were measured by enzyme immunoassay (EIA and ELISA) (Diagnostic Automation INC., Calabasas, CA, USA). Insulin was also determined by ELISA assay (Diagnostic Automation INC., Calabasas, CA, USA). Plasma glucose and uric acid levels were measured with commercial enzymatic kits (Aeroset; Abbott Laboratories, Abbot, IL, USA).

Homeostasis model assessment (HOMA-IR) was calculated from fasting insulin and glucose levels using the formula = fasting insulin (µUI/mL) x fasting glucose (mmol/L)/22.5.

In all hormonal assays, the intra and inter-assay coefficient of variation was <12%.

Statistical analysis

All analyses were performed with PASW Statistics 18 (former SPSS Statistics). For statistical data analysis non-parametric tests were used (Mann-Whitney). Analysis of sequences of values for the two study groups (PCOS and non-PCOS) in order to establish statistical correlations was performed by calculating the Spearman correlation coefficients. A correlation was considered statistically significant if the threshold for statistical significance was $p<0.05$. Multiple linear regression analysis using a stepwise method for the introduction of independent variables was used to identify the main determinants of uric acid levels among the variables showing a statistically significant correlation with this marker.

Results

Women in the two groups (PCOS and non-PCOS) had comparable BMI (median value 34 vs. 32.74 kg/m²) and age (median value 31.5 vs. 35.5 years). Compared with controls, women with PCOS had significantly higher levels of LH (median value 6.4 vs. 4.15 mUI/mL, $p<0.01$), testosterone (median value 1.5 vs. 0.3 ng/dL, $p<0.001$), fasting insulin (median value 12.45 vs. 8.95 µUI/mL, $p<0.01$), and HOMA-IR (median value 2.93 vs. 2.05, $p<0.05$) (Table I).

Table I. Anthropometric variables, hormonal parameters, insulin resistance (calculated by HOMA) and uric acid in PCOS and non-PCOS women

Test Statistics[a]

	Fasting glucose	Fasting insulin	HOMA-IR	Uric acid	FSH	LH	Testosterone	Waist	BMI	Age
Mann-Whitney U	455.0	307.5	394.00	528.50	528.00	294.5	149.50	458.50	559.5	474.0
Wilcoxon W	1196.0	772.5	859.00	993.50	1269.0	759.5	614.50	1199.5	1300.5	1215.0
Z	-1.421	-3.243	-2.174	-0.513	-0.519	-3.40	-5.205	-1.379	-0.130	-1.190
Asymp. Sig. (2-tailed)	0.155	0.001	0.030	0.608	0.604	0.001	0.000	0.168	0.897	0.234

a.Grouping variable: patients PCOS and non-PCOS (Mann-Whitney test)

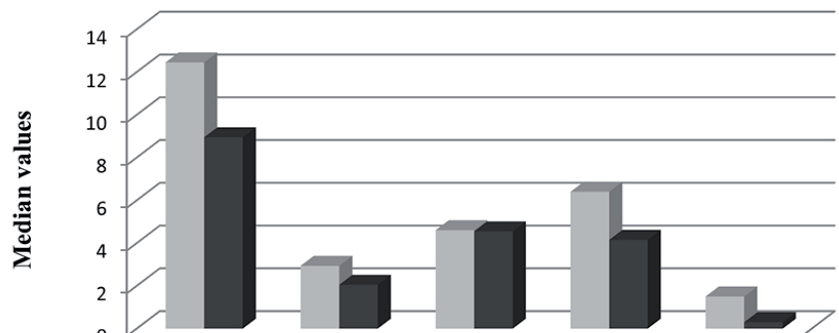
Serum uric acid levels did not differ significantly in the two study groups, as seen in the figure below (median value 4.6 mg/dL in PCOS group vs. 4.55 mg/dL in non-PCOS group) (Fig. 1). Also, no statistically significant differences were found between glucose levels (median value 97.5 vs. 98.5 mg/dL) and waist circumference (median value 105.5 vs. 105 cm) in the two study groups (PCOS and non-PCOS).

Plasma uric acid levels correlated directly with BMI ($r = 0.683$, $p<0.001$), waist circumference ($r = 0.485$, $p<0.01$), insulin ($r = 0.518$, $p<0.01$) and HOMA-IR ($r = 0.479$, $p<0.01$) in PCOS women (Fig. 2). In non-PCOS group, we also found a weaker, but still significant positive correlation between serum uric acid levels and BMI ($r = 0.385$, $p<0.05$), waist circumference ($r = 0.446$, $p<0.05$), insulin ($r = 0.447$, $p<0.05$), and HOMA ($r = 0.451$, $p<0.05$). No correlation between uric acid levels and testosterone or LH was found. Following the use of stepwise linear regression analysis, the only parameter retained by the regression model was BMI, responsible for 42.1% of the variability of serum uric acid levels.

Discussion

Previous studies have shown that uric acid may increase the risk for cardiovascular disease through its inflammatory, proliferative and oxidative actions at the endothelial level (8). There is a correlation between the elevated uric acid concentration and cardiovascular events in patients at high risk, unlike the general population (14). Years ago, Johnson et al. demonstrated a pathogenic role for uric acid in hypertension, renal and cardiovascular disease (15). Moreover, the decrement in serum uric acid concentration after inhibition of xanthine-oxydase with allopurinol has led to an improvement of endothelial function (16, 17).

During the past years, it has become evident that alterations in insulin action are frequent in women with PCOS (18-24). About 60%-70% of PCOS patients present central obesity that is well known to be associated with insulin resistance and increased risk of type 2 diabetes mellitus, hypertension, dyslipidemia, endothelial dysfunction and heart disease (25). In association with insulin resistance, obesity contributes to the



	fasting insulin (µUI/mL)	HOMA -IR	Uric Acid (mg/dL)	LH (mUI/mL)	Testosterone (ng/dL)
PCOS Median	12.45	2.935	4.6	6.4	1.5
non-PCOS Median	8.95	2.05	4.55	4.15	0.3

Figure 1. Parameters variation according to their median value for studied groups (PCOS and non-PCOS) (Mann-Whitney test)

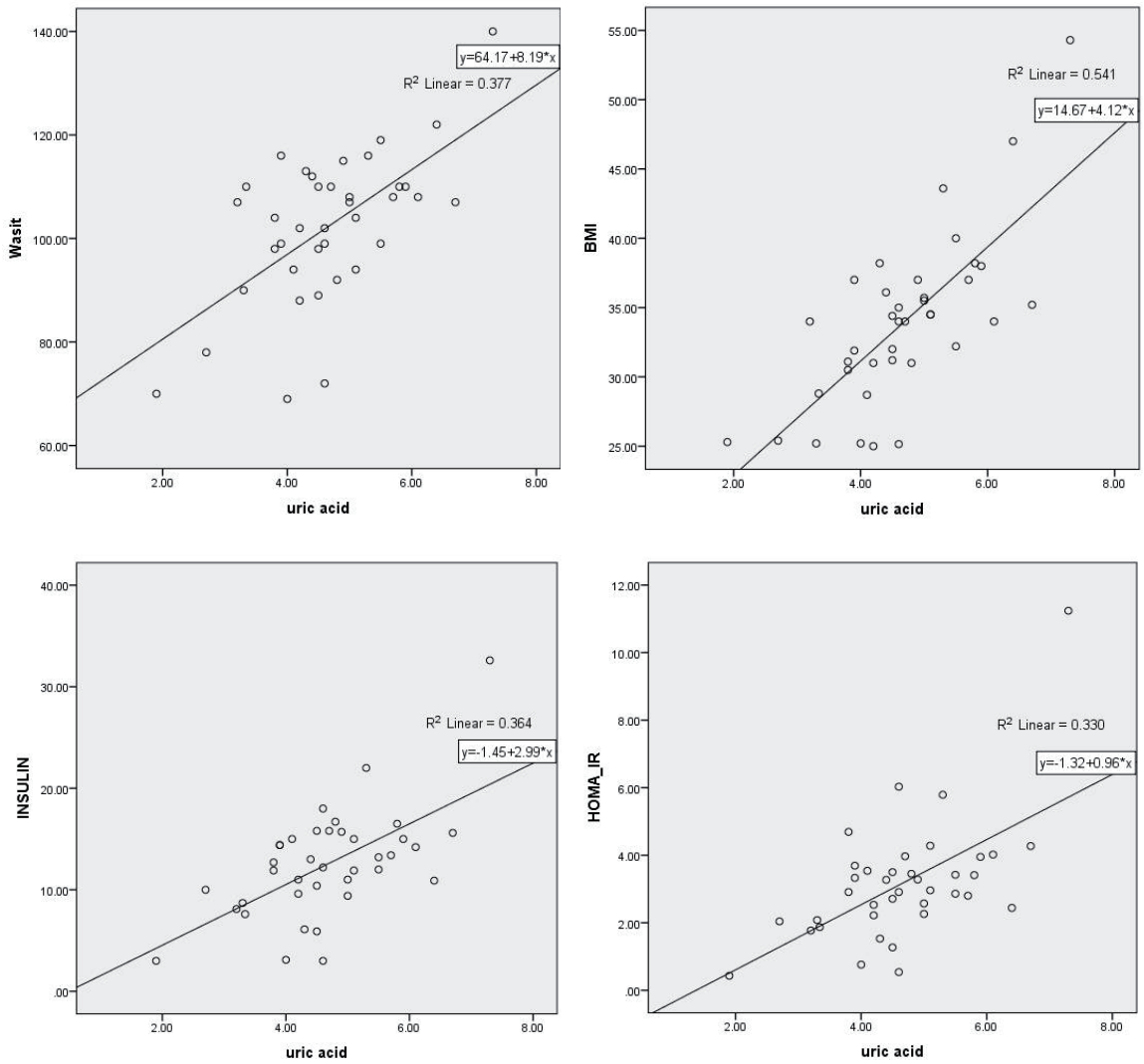


Figure 2. Correlation between serum uric acid and BMI, waist circumference, insulin and HOMA-IR for PCOS patients. The Spearman correlation test was used

40% prevalence of the metabolic syndrome in PCOS (26-33).

Recent data have shown a complex correlation between insulin resistance and inflammation. Subclinical inflammation and insulin resistance are important risk factors that may predict cardiovascular disease (34, 35).

Hyperinsulinism inhibits the excretion of uric acid in the kidney and also increases sodium reabsorption, thus explaining, even if only partially, the association between insulin resistance, obesity, and elevated serum uric acid levels (11, 15). Even so, the role of uric acid as cardiovascular risk marker remains controversial (36).

The use of uric acid as a cardiovascular risk marker in PCOS is related to the question whether androgens might influence to some extent serum uric acid levels. The possible link between androgens and serum uric acid levels is supported by many findings. In a recent study, Luke-

Ramirez et al. have found increased levels of uric acid in men compared to women (11). Also, older studies of nearly 20 years ago, supported by newer ones have shown that in animal models serum uric acid concentrations may be increased by androgens, which have an important role in the hepatic metabolism of purines (37, 38).

The results of many studies available until now are controversial. One of the first studies that have analyzed the utility of serum uric acid determination for the screening of metabolic syndrome in PCOS was conducted almost 20 years ago, and its results were not encouraging. The authors found no differences between serum uric acid in PCOS women compared with controls. On the other hand, they found a positive correlation between insulin levels and serum uric acid concentrations in PCOS group, suggesting a possible correlation between insulin sensitivity and serum uric acid levels (10). In a more recent study, no differences were observed between PCOS and non-PCOS women (with similar BMI) regarding plasma uric acid concentrations (11).

The findings of our study confirm that serum uric acid levels are not increased in PCOS patients when compared with normal controls matched for age and BMI. Although women with PCOS were more hyperandrogenic and more insulin resistant than non-PCOS women, it seems that these factors have not yet influenced uric acid levels.

The plasma levels of uric acid positively correlated in PCOS and non-PCOS group with BMI, waist circumference, and also with insulin and HOMA. When all these variables were used to predict the uric acid level using linear regression analysis, BMI remained the only determinant of uric acid level, responsible for 42.1% of its variability. Our results suggest that obesity, and not insulin resistance is the main determinant of uric acid in women with PCOS.

These findings are consistent with those published by Luque-Ramirez et al. (11), which have shown that BMI accounts for a rate of 35.4% of the variability in plasma uric acid concentrations in premenopausal women.

Although most women in our study had normal uric acid levels, the influence of obesity is crucial due to the fact that any increase in uric acid concentrations is associated with a high rate of cardiovascular mortality (11, 39).

Uric acid correlations with waist circumference, insulin and HOMA suggest a possible less important contribution of these factors in its regulation.

To our knowledge, this is the first study in our country analyzing the levels of uric acid in obese and overweight women with PCOS. A limitation of our study is the small sample size that may contribute to a lack of statistical power. Another potential limitation is the fact that all patients (PCOS and controls) were overweight and obese. It would be interesting and useful to analyze these parameters in normal weight women with PCOS compared with normal weight controls.

Conclusions

Our results have shown that compared with weight- and age-matched controls, in women with PCOS, obesity is the main factor responsible for uric acid levels. It is possible that other factors such as abdominal obesity, insulin resistance and inflammatory markers to play a role in this mechanism, fact that remains to be clarified in further studies.

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Abbreviations

PCOS - polycystic ovary syndrome
BMI - body mass index
HOMA-IR - homeostasis model assessment of insulin resistance
FSH – follicle-stimulating hormone
LH - luteinizing hormone
EIA – enzymatic immunoassay
SD – standard deviation

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