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## Serum Uric Acid Concentration in Patients with Polycystic Ovary Syndrome Treated by Metformin

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### Abstract:

**Background:** Serum uric acid levels have emerged as a cardiovascular risk factor, and interventions aimed to decrease its level have been related with an improvement in clinical and non-clinical cardiovascular outcomes. This is particularly strong among persons at high cardiovascular risk, including those with hypertension, diabetes or polycystic ovary syndrome (PCOS). The studies about the effect of metformin on serum uric acid in patients with PCOS are very scarce at least in our locality.

**Objective:** To evaluate the effect of metformin on serum uric acid concentration as non-classical cardiovascular risk factor in patients with PCOS in Mosul City in Iraq.

**Design:** Case control study, Study Period: From 1<sup>st</sup> of November 2010 and 1<sup>st</sup> April 2011.

**Patients & Methods:** A group of 40 women with PCOS of reproductive age who used metformin for more than three months (metformin users), with another age- and body mass index (BMI)-matched group of 52 women with PCOS who did not use metformin (metformin non-users), were included in this study. From each patient, a 5 ml blood sample was taken. The serum was used to measure the S.UA level using commercially available kit. BMI calculated as weight in kilograms divided by the squared height in meters.

**Results:** This study revealed a significant lower levels of serum uric acid ( $P = 0.045$ ) in metformin users as compared with metformin non-users and the serum uric acid levels were significantly correlated with BMI ( $r = 0.326$ ,  $P = 0.001$ ), systolic blood pressure (SBP) ( $r = 0.283$ ,  $P = 0.006$ ) and diastolic blood pressure (DBP) ( $r = 0.301$ ,  $P = 0.003$ ) when the whole study population was taken.

**Conclusion:** Metformin therapy for more than three months in patients with PCOS is associated with significantly lower levels of serum uric acid and these levels are significantly related to BMI, SBP, and DBP.

**Key words:** polycystic ovary syndrome, metformin, uric acid.

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### Introduction:

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age that affects about one in 15 women worldwide. It is the main cause of anovulatory infertility in women, and is associated with several comorbidities<sup>1</sup>. In the past two decades, it has become apparent that PCOS is highly associated with features of the metabolic syndrome, including obesity, insulin resistance and dyslipidemia, which are risk factors for cardiovascular disease (CVD)<sup>1,2</sup>.

Uric acid is a metabolic product of purine metabolism that may function as an antioxidant<sup>3</sup> owing to its ability to chelate transition metal ions and to react with biological oxidants such as hydroxyl radicals<sup>4</sup>. However, it must be considered that under certain conditions, the formation of uric acid is connected to the conversion of xanthine dehydrogenase (XDH) to xanthine oxidase (XO) which leads to concomitant production of free radicals<sup>5</sup>. Therefore, Uric acid exerts proinflammatory, prooxidant and proliferative actions at the endothelial cell level that may increase cardiovascular (CV) risk<sup>6</sup>.

Previous studies had indicated that the development of metabolic syndrome due to a cluster of CVD risk factors correlates with alterations in serum uric acid levels<sup>4,7</sup>. Also, in a study of Vuorinen-Markkola and Yki-Jarvinen<sup>8</sup> demonstrated an inverse

correlation between serum uric acid (S.UA) concentration and insulin sensitivity in patients with metabolic syndrome and they concluded that hyperuricaemia is an inherent biochemical feature of this syndrome, and suggested hyperuricaemia to be a simple marker of insulin resistance. As PCOS is considered a variant of the metabolic syndrome<sup>9</sup> for these reasons, serum uric acid levels are anticipated to be high in women with PCOS. However, the studies available at present regarding serum uric acid levels in PCOS patients are scarce and led to controversial results<sup>10,11,12,13</sup>.

Oral contraceptives have been the mainstay of pharmacological treatment of PCOS for decades<sup>2</sup>. However, in non-hyperandrogenic women oral contraceptives might adversely influence insulin resistance and glucose tolerance, raising concern about a possible worsening of the already unfavorable metabolic cardiovascular risk profile of PCOS patients and favoring the use of the metabolically safer insulin sensitizer drugs<sup>14</sup>. Metformin was first used in women with PCOS by Velazquez *et al.*,<sup>15</sup> and found to have beneficial reproductive and metabolic effects in PCOS, which was supported by several subsequent studies<sup>16,17</sup>. For these purposes we have studied here the serum uric acid concentrations of well-defined populations of PCOS patients taking insulin sensitizer metformin as compared to another age- and BMI-

matched group of PCOS patients who did not taken metformin to see the effect of this insulin sensitizer on serum uric acid as a non-classic cardiovascular risk marker. To our knowledge, this was the first study of kind at least in our locality.

**Patients and Methods:**

This study was carried out between 1<sup>st</sup> of November 2010 and 1<sup>st</sup> April 2011 in Fertility and *In vitro* fertilization Center in Mosul, and at the fertility & sterility clinic in the Medical Center that belongs to Mosul Medical College. Both are located at the right bank of the river Tigris in Mosul city, Iraq. To achieve the aims of the present study, a case-control study design was adopted. Ninety-two women at child-bearing age, diagnosed with PCOS were enrolled for this study. PCOS was defined according to the Rotterdam 2003 criteria<sup>18</sup> i.e. when two (or more) of the three of the following criteria were found: oligo- and/or anovulation; clinical and/or biochemical hyperandrogenism; polycystic ovaries (PCO), and exclusion of other etiologies. These participants were divided into two groups. The metformin users group comprised 42 women with PCOS (age ranged 17-38 years) that were taking metformin (Metforal<sup>®</sup> tablets . provided by Menarini International Pharmaceutical Industries, Florence – Italy) of doses (ranged 1000 to 1700 mg daily) for durations ranged from 3 to 18 months. Patients who had diabetes mellitus, hyperprolactinemia, congenital adrenal hyperplasia, thyroid disorders, Cushing’s syndrome, hypertension, vitamin B12 and folate deficiency, hepatic or renal dysfunction, smoking habit, past or current history of CVD were excluded from the study. None of the patients was treated with hormonal contraceptives, antihypertensive drugs, aspirin, statins, or any other medication (except for metformin) for at least 6 months before blood examination. Metformin non-users group consisted of 52 women with PCOS (age ranged from 18-40 years), who had similar criteria as the metformin users except that they did not take metformin.

Anthropometric measures (body weight (Kg) and height (cm)) were taken. Weight and height were measured in light clothing without shoes. Waist

circumference was measured at the narrowest level between the costal margin and the iliac crest, and the hip circumference was measured at the widest level over the buttocks while the subject was standing and breathing normally. The BMI was calculated as weight in kilograms divided by the square of height in meters<sup>19</sup>. The studied PCOS patients (with and without metformin therapy) classified according to BMI. BMI  $\geq 30$  were considered obese, while BMI  $< 30$  were considered non-obese<sup>20</sup>. The blood pressure was measured for each subject by a mercury sphygmomanometer in the sitting position after a rest of at least 10 minutes.

Five ml of venous blood were withdrawn from PCOS patients, using a disposable syringe after 12-hour fasting, the serum was kept frozen at -20 °C to be analyzed. Serum uric acid was measured by the enzymatic colorimetric method, using kit supplied by (Randox Laboratories Ltd., UK).

Standard statistical methods were used to determine the mean and standard deviation (SD). Unpaired *t*-test was used to assess the significance of differences of levels of S.UA, diastolic blood pressure (DBP) and systolic blood pressure (SBP), as well as ages, waist-to-hip ratio (WHR), BMI between metformin users and metformin non-users groups. Pearson correlation coefficients were used in correlation analyses. All values quoted as the mean  $\pm$  SD and P-value  $\leq 0.05$  was considered to represent statistical significance.

The approval of the study protocol by an ethic committee has been obtained from the local health committee of Ministry of Health and College of Medicine - University of Mosul – Iraq.

**Results**

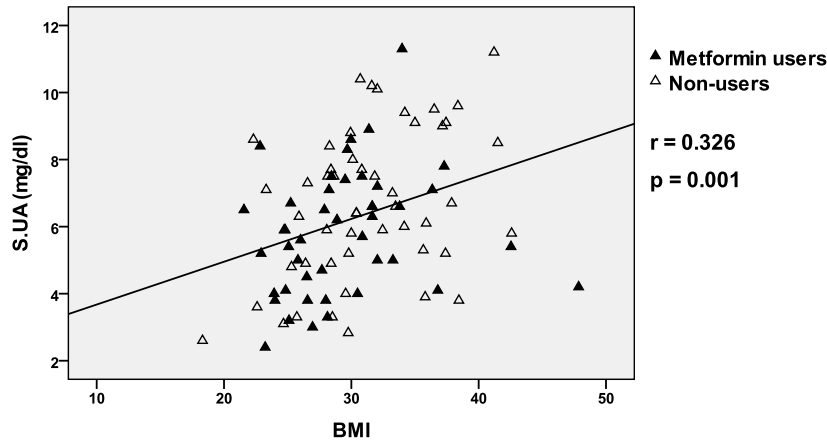
A statistically non-significant differences had been demonstrated between metformin users group of patients with PCOS in comparison with metformin non-users concerning age, BMI, WHR, SBP, and DBP, but a significant difference had been observed in the serum levels S.UA when both groups were put under comparison as shown in table 1.

Table 1 : The mean $\pm$ SD values of parameters of metformin and metformin non-users groups.

Variables	Metformin users N=42	Metformin non-users N=51	P-value
Age (years)	26.67 $\pm$ 5.14	26.35 $\pm$ 5.596	0.781(NS)
BMI (kg/m <sup>2</sup> )	29.393 $\pm$ 5.334	31.201 $\pm$ 5.301	0.106 (NS)
WHR	0.843 $\pm$ 0.076	0.842 $\pm$ 0.072	0.939(NS)
SBP (mmHg)	118.16 $\pm$ 10.49	120.66 $\pm$ 8.45	0.206(NS)
DBP (mmHg)	76.45 $\pm$ 9.84	79.65 $\pm$ 7.51	0.088(NS)
S.UA (mg/dl)	5.8 $\pm$ 1.891	6.673 $\pm$ 2.194	0.045

According to BMI, about half (51.04 %) of the studied PCOS patients (with and without metformin therapy) found to be obese and about half (48.96 %) found to be non obese. The results revealed that there was significant direct positive correlation between S.UA

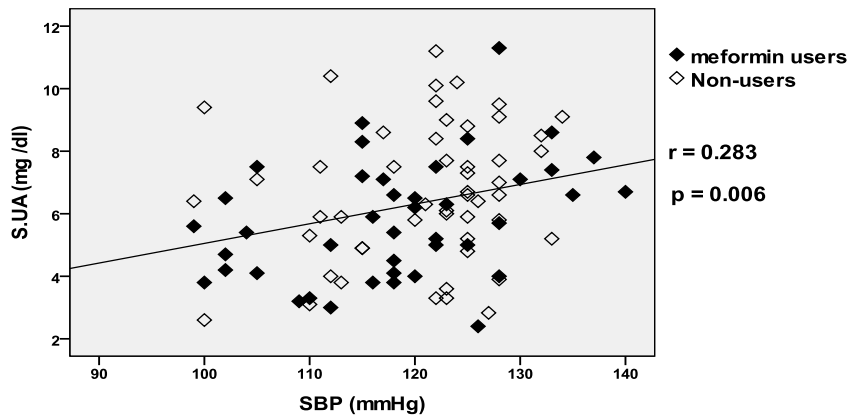
levels and BMI when the study population was taken as a whole with Pearson correlation coefficient ( $r$ ) equal to 0.326 and  $P$ -value equal to 0.001 as shown in figure 1.



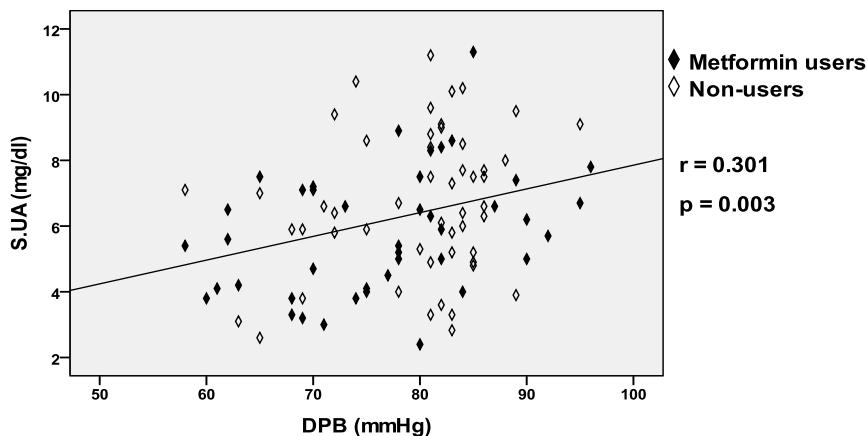
**Figure 1:** Correlation between S.UA levels and BMI in the studied whole PCOS population

Figure 2 shows a significant direct positive correlation between S.UA levels and SBP when the study population was taken as a whole ( $r = 0.283$  and  $P =$

0.006), whereas figure 3 shows a significant direct positive correlation between S.UA levels and DBP ( $r = 0.301$ ,  $P = 0.003$ ).



**Figure 2:** Correlation between S.UA levels and SBP in the studied whole PCOS population



**Figure 3:** Correlation between S.UA levels and DBP in the studied whole PCOS population

## Discussion

The rationale for the use of an insulin sensitizing drug, such as metformin, in treatment of patients with PCOS arises from the knowledge that insulin resistance with compensatory hyperinsulinemia has provided an insight into the pathogenesis of PCOS, although, not an essential criteria for the diagnosis of PCOS<sup>21</sup>. The followed clinical studies have shown that administration of metformin to women with PCOS resulted in improvement of clinical and biochemical signs of hyperandrogenism, increased rate of ovulation, restoration of regular menses, and enhanced ovulatory response to clomiphene<sup>16,17</sup>.

This study revealed that there were a significant lower S.UA levels in patients with PCOS treated with metformin in comparison to those who did not receive metformin therapy, this may indicate that insulin resistance- to some extent- could affect the S.UA levels in PCOS patients. But other studies like those conducted by Lord *et al.*,<sup>22</sup> and Luque-Ramirez *et al.*,<sup>13</sup> are not in agreement with this finding.

It could be argued that the magnitude of the changes in serum uric acid levels during treatment with metformin in our PCOS patients was small and occurred within the normal range in most cases. Yet increases in uric acid concentrations as small as 59 µmol/l increase the frequency of cardiovascular events and ischemic cardiopathy<sup>23</sup>. Moreover, 29% of the decrease in the primary outcome cardiovascular death, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke observed in the arm of treatment with losartan in the LIFE study was attributed to the reduction observed in serum uric acid levels secondary to the uricosuric properties of this drug<sup>24</sup>, highlighting the possible cardiovascular benefits of controlling and reducing uric acid concentrations.

In this study, S.UA levels were found to be significantly correlated to BMI, SBP and DBP. The study of Luque-Ramirez *et al.*,<sup>13</sup> also found that main determinant of serum uric acid level in patient with PCOS was the body mass. The well-known association of increased S.UA levels, obesity, and insulin resistance is partly explained by the inhibitory action of hyperinsulinism on the renal excretion of uric acid<sup>25</sup>. Besides, the influence of obesity on these levels is important because increasing serum uric acid levels associates' increased cardiovascular mortality even with values within the normal range<sup>26,27</sup>.

Several lines of recent evidence suggest that an association between serum uric acid and hypertension is plausible, including the direct role of uric acid in vascular smooth muscle cell proliferation<sup>28</sup>, endothelial dysfunction and decreased nitric oxide production, proinflammatory features of soluble uric acid<sup>29</sup>, local activation of renin-angiotensin system<sup>30</sup>

and its relation to insulin resistance and components of the metabolic syndrome<sup>31</sup>.

Conclusion: Metformin use for more than 3 months in patients with PCOS is associated with significantly lower S.UA levels and that S.UA levels in these patients are significantly related to BMI, SBP and DBP.

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