

## C-reactive protein and lipid profile in patients with polycystic ovary syndrome treated by metformin

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### ABSTRACT

**Objective:** To evaluate the effect of metformin on serum hs-CRP levels and lipid profile in patients with PCOS in Mosul City in Iraq.

**Methodology:** This is a case control study conducted at the Fertility and Sterility Clinic in the Medical Center that belongs to Mosul Medical College / Iraq, from the 1<sup>st</sup> of November 2009 to the 15<sup>th</sup> May 2010. A group of 43 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 53 women with PCOS who did not use metformin (metformin non-users), were included in this study. From each patient, a 10 ml fasting venous blood sample was taken. The serum was used to measure the biochemical parameters using commercially available kits, whereas serum low-density lipoprotein cholesterol (LDL-c) was calculated using Friedewald equation. Atherogenic index (AI) was recognized by simple equation and BMI was calculated as weight in kilograms divided by the squared height in meters.

**Results:** This study revealed a significant lower level of hs-CRP ( $P = 0.04$ ) in metformin users as compared with metformin non-users. There were a significant lower levels of total cholesterol (TC) ( $P = 0.003$ ), LDL-c ( $P < 0.001$ ), AI ( $P < 0.001$ ) and significantly higher levels of high-density lipoprotein cholesterol (HDL-c) ( $P = 0.026$ ) in metformin users when compared with metformin non-users, but a non significant reduction in triglycerides (TG) level between the two groups of patients.

**Conclusion:** Metformin therapy for more than three months seems to have beneficial and a favorable effects on both lipid profile and hs-CRP serum level respectively in patients with PCOS.

**KEY WORDS:** Polycystic ovary syndrome, Lipid profile, C-reactive protein.

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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 co-morbidities.<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>1-3</sup>

The rationale for the use of an insulin sensitizing drug, such as metformin, in the 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>4</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 menstrual cycle, and enhanced ovulatory response to clomiphene.<sup>5-7</sup>

C-reactive protein (CRP), is an acute phase protein.<sup>8</sup> In addition, increased hs-CRP levels may identify patients at increased cardiovascular risk.<sup>9</sup> Morin-Papunen et al,<sup>10</sup> demonstrated that serum concentrations of CRP were significantly higher in obese than in non-obese PCOS subjects at baseline suggesting that the elevated CRP levels may be related to obesity and not only to PCOS itself. They also reported a significant reduction in serum CRP levels at 6-months treatment with metformin in the whole study population.

In a study conducted in Bosnia by Velija-Asimi<sup>11</sup> in 35 obese women with PCOS aged 20-35 years showed that the mean serum CRP levels significantly decreased after one year treatment with metformin. The study performed by Tsilchorozidou et al<sup>12</sup>, found that after six weeks of metformin therapy there was a significant reduction in CRP levels, while at 6 months there was a significant reduction of Interleukin-6 levels with no further reduction of CRP. However, CRP levels were not significantly affected by 12 weeks therapy of metformin when compared with placebo in a study conducted by Agarwal et al.,<sup>13</sup> on a thirty women with PCOS.

Dyslipidemia is possibly the most common metabolic abnormality of PCOS, although the findings of relevant studies have been variable and a substantial percentage of women with PCOS might still have normal lipid profiles.<sup>14</sup> In a study conducted in Mosul city, by Shamdeen and Mohammad,<sup>15</sup> to assess 50 infertile Iraqi women with PCOS clinically and biochemically, TG, TC, LDL-c levels and AI were found to be significantly higher in PCOS group and the highest value was observed in overweight subjects. HDL-c levels were significantly lower in PCOS groups but no significant differences within PCOS groups were observed.

Atherosclerotic vascular disease is less frequent in premenopausal women than in men, which may be attributed to differences in sex steroids. In addition, there is some evidence that in men, testosterone is a key factor regulating HDL levels and composition.<sup>16</sup> Since women with PCOS frequently have elevated plasma androgens, male pattern dyslipidemia is common in PCOS women, although

the extent and type of dyslipidemia is variable.<sup>14,16</sup> Dyslipidemia in PCOS patients has been observed in many studies.<sup>15-18</sup> The majority of these studies share the fact that PCOS is associated with significantly elevated TC, LDL-c and TG levels with concomitantly reduced concentration of HDL-c as compared to healthy women with regular menstrual periods. Metformin therapy used for PCOS for a variable periods showed a variable effects on lipid profile parameters.<sup>19-23</sup>

The aims of the present study were to assess the effect of metformin therapy for more than three months on serum levels of hs-CRP and lipid profile (serum TC, HDL-c, LDL-c, TG and AI) in a group of women with PCOS on metformin therapy in comparison with age- and BMI-matched PCOS patients without metformin therapy.

## METHODOLOGY

This case-control study was conducted in the Fertility and 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 in Iraq. From the 1<sup>st</sup> of November 2009 to 15<sup>th</sup> May 2010. This study included ninety-six women at child-bearing age, diagnosed with PCOS according to the Rotterdam 2003 criteria<sup>24</sup> were enrolled for this study. These participants were divided into two groups, the metformin users included 43 women with PCOS (age ranged from 17-38 years) on metformin therapy (Metforal<sup>®</sup> tablets provided by Menarini International Pharmaceutical Industries, Florence - Italy) of doses (ranged from 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, and infectious diseases were excluded from the study. None of the patients was treated with hormonal contraceptives, antihypertensive drugs, aspirin, statins, or any other medication for at least two months before blood examination. Metformin non-users group consisted of 53 women with PCOS (age ranged from 18-42 years), who had similar criteria as the metformin users except that they did not take metformin.

Anthropometric measures (blood pressure (mmHg), body weight (Kg) and height (cm)) were taken. The BMI was calculated as weight in kilograms divided by the square of height in meters.<sup>25</sup> The studied PCOS patients (with and without met-

formin therapy) classified according to BMI. BMI  $\geq 30$  were considered obese, while BMI  $< 30$  were considered non-obese.<sup>26</sup>

Ten ml of venous blood were withdrawn from PCOS patients after 12-hour fasting, the serum was separated and kept frozen at  $-20^{\circ}\text{C}$  to be analyzed for determination of serum glucose level by enzymatic colorimetric method using Randox kit (Randox Laboratories Ltd., UK). Serum hs-CRP was measured by enzyme linked immunosorbent assay (ELISA) technique, using the AccuBind hs-CRP ELISA kit- supplied by Monobind Inc., Lake Forest, California, USA. Measurement of serum TC and TG concentration was done by the enzymatic colorimetric method, using a special kit for each supplied by (Randox Laboratories Ltd., UK), while serum HDL was measured by the precipitation method, using HDL Cholesterol/ Phospholipids kit supplied by (Randox Laboratories Ltd., UK). Serum LDL was calculated by using Friedewald equation.<sup>27</sup>  $\text{LDL (mmol/l)} = \text{TC} - \text{HDL} - (\text{TG}/2.19)$ . Atherogenic index (AI) was calculated by the following equation:  $\text{AI} = \text{TC} / \text{HDL}$ .<sup>28</sup>

The data obtained in the current study was analyzed using predictive analytic software (PASW) version 18, which was formerly called SPSS. Standard statistical methods were used to determine the mean and standard deviation (SD). Student's unpaired t-test was used to compare the results of various biochemical parameters between the two groups of PCOS patients. Linear regression analysis [Pearson correlation coefficient (r)] was performed in the total population to identify the relationships between different parameters. All values quoted as the mean  $\pm$  SD and P-value  $\leq 0.05$  was considered to represent statistical significance be statistically significant.

The approval of the study protocol by an ethic committee was obtained from the local health committee of Ministry of Health and College of Medicine, University of Mosul, Mosul, Iraq.

### RESULTS

A total number of 43 women with PCOS who used metformin for more than three months were included in this study, (with mean age  $\pm$  SD of  $26.70 \pm 5.08$ ), those have been considered to represent the exposed group (metformin users) group. Another 53 women with PCOS (with mean age  $\pm$  SD of  $26.68 \pm 5.89$ ), who did not use metformin were considered to represent metformin non-users group.

According to BMI, about half (51.04%) of the studied PCOS patients (with and without metformin

Table-I: Comparison between serum hs-CRP levels in metformin users and non-users.

Parameters	Mean $\pm$ SD		P-value
	Metformin users (n= 43)	Metformin non-users (n= 53)	
hs-CRP	7.59 $\pm$ 8.66	12.38 $\pm$ 12.89	0.004

Table-II: Comparison between lipid profile in metformin users and non-users.

Parameters	Mean $\pm$ SD		P-value
	Metformin users (n= 43)	Metformin non-users (n= 53)	
TC (mg/dl)	164.03 $\pm$ 30.38	187.25 $\pm$ 40.78	0.003
HDL-c (mg/dl)	47.47 $\pm$ 8.91	43.31 $\pm$ 8.98	0.026
LDL-c (mg/dl)	97.63 $\pm$ 26.25	121.63 $\pm$ 37.87	<0.001
TG (mg/dl)	94.69 $\pm$ 72.59	111.54 $\pm$ 55.52	NS
AI	3.577 $\pm$ 0.936	4.502 $\pm$ 1.309	<0.001

in therapy) found to be obese. There were no significant differences in the mean age, weight, BMI, waist to hip ratio (WHR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) of the metformin users and non-users. Also no significant difference between fasting serum glucose levels in metformin users and non-users.

This study demonstrated a significant lower serum hs-CRP level in the metformin users group in comparison to the non-users group (Table-I).

This study revealed a significant lower serum TC, LDL-c and AI, and higher serum HDL-c in metformin users when compared with non-users with a non significant reduction in the serum TG levels between the two groups (Table-II).

There was a highly significant positive correlation ( $r=0.478$ ;  $P<0.001$ ) between BMI and hs-CRP in patients with PCOS (with and without metformin therapy) as shown in Fig.1.

There was a highly significant positive correlation ( $r=0.409$ ;  $P<0.001$ ) between BMI and AI in patients

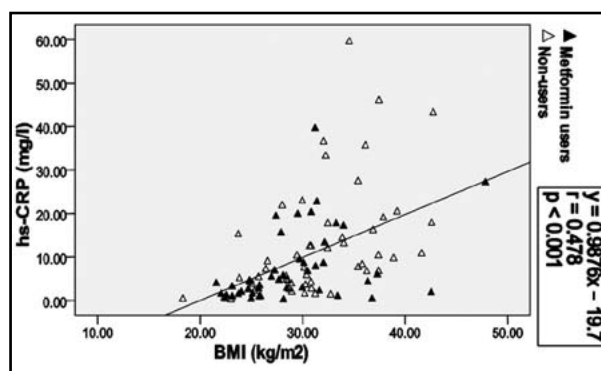


Fig.1: Relationship between BMI and CRP in the studied patients.

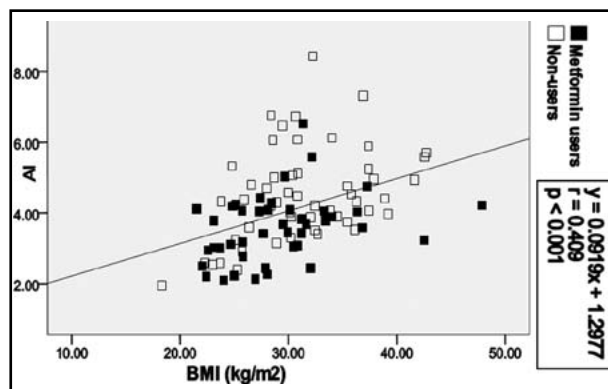


Fig.2: Relationship between BMI and AI in the studied patients.

with PCOS (with and without metformin therapy) as shown in Fig.2.

There was a highly significant positive correlation ( $r=0.272$ ;  $P=0.007$ ) between AI and hs-CRP in patients with PCOS (with and without metformin therapy) as shown in Fig.3.

## DISCUSSION

This study found no-significant differences in the FSG level between the two PCOS groups of patients involved in this study. This non-significantly differed FSG supports the idea which tells that metformin has little effect on blood glucose in non-hyperglycemic subjects.<sup>29</sup> In a study performed by Carmina et al.,<sup>30</sup> to assess the difference between US (United States) PCOS patients and Italian PCOS patients concerning the weight and the influence of diet, they found the percentage of obese amongst US PCOS to be 69% and in the Italian group of women to be 38%. In the present study, the percentage of obese in the whole study population found to be about 51%, which is approximately in the middle between the above-mentioned two values.

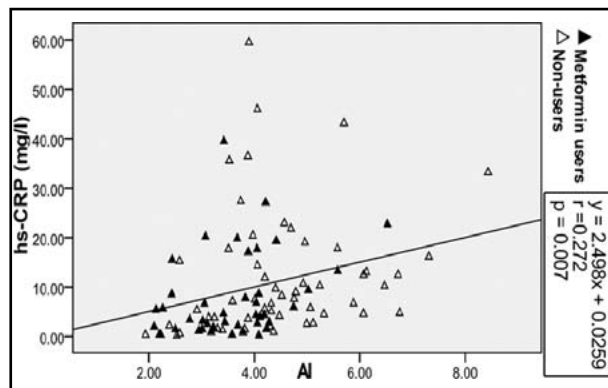


Fig.3: Relationship between AI and hs-CRP in the studied patients.

In the present study, it was observed that the serum hs-CRP levels were significantly lower in patients with PCOS who use metformin for more than three months as compared to age- and BMI-matched group of PCOS women without metformin therapy. This finding is in agreement with other studies<sup>10,31</sup> which reported a significant reduction in serum CRP levels at 6-months and after one year<sup>11</sup> treatment with metformin therapy in PCOS women. However Tsilchorozidou et al.,<sup>12</sup> found a significant decrease in CRP concentrations after 6 weeks of metformin therapy, and no further significant reduction was noted at 6-months therapy, while Agarwal et al.,<sup>13</sup> showed that the mean CRP levels of thirty women with PCOS were not significantly affected by 12 weeks therapy of metformin when compared with placebo.

In this study, hs-CRP was significantly and positively related to BMI ( $r=0.478$ ;  $P<0.001$ ) in PCOS patients (with and without metformin therapy). This suggests that the increased CRP levels found in women with PCOS may be related to obesity and not just to PCOS. Such a strong correlation was also observed in PCOS women in many studies.<sup>10,12,31,32</sup>

In the current study, TC levels found to be significantly lower in PCOS patients taking metformin for more than three months against those without metformin therapy and this result is similar to those conducted by Aruna et al.,<sup>21</sup> and Banaszewska et al.,<sup>23</sup> but contrary to the results obtained by Fleming et al.,<sup>19</sup> Cheang et al.,<sup>20</sup> and Orio et al.<sup>22</sup>

Also in the present study, HDL-c was noted to be significantly elevated in PCOS women with metformin therapy when compared with their counterpart PCOS subjects who did not have metformin. Such finding is compatible with the results of several studies.<sup>19-22</sup> However, the study of Banaszewska et al.,<sup>23</sup> did not agree with this.

Another finding from the present study was that, LDL-c seemed to be significantly low in PCOS subjects with metformin treatment for more than three months in comparison with their age- and BMI-matched PCOS patients without metformin therapy. This resembles the results observed by Orio et al.<sup>22</sup> and Banaszewska et al.<sup>23</sup> but are contrary to the findings of other studies.<sup>19-21</sup> The AI in this study was significantly low in metformin users as compared with metformin non-users, which is in agreement with other studies<sup>21,23</sup> in this regard.

This study, however, did not find a significant difference in TG levels between both groups of PCOS patients. This non-significant difference

was also found by other studies.<sup>19-22</sup> In contrast to this finding, Banaszewska et al.,<sup>23</sup> stated that TG levels were significantly decreased in women with PCOS after 6-months treatment with metformin. These results of this study regarding lipid profile indices were also consistent with the opinion which says that metformin have favorable effects on lipid profile.<sup>29</sup> A study done by Bass et al.,<sup>33</sup> demonstrated that both HDL-c and TG were better predictors of coronary risk and cardiovascular mortality in women than TC or LDL-c. A meta-analysis performed by Hokanson and Austin<sup>34</sup> supported these data by showing that an increase in triglycerides of 1 mmol/l was associated with a 76% increased risk of cardiovascular disease in women versus 32% in men.

The present study also clarified a highly significant direct correlation between BMI and AI (as a logical representative of lipid profile) in PCOS women (with and without metformin therapy), and according to this, it is apparent that BMI was an important predictor of lipid profile. This significant relationship was also found in a study conducted by Banaszewska et al.<sup>23</sup>

In this study, AI was found to be directly and significantly correlated with hs-CRP in patients with PCOS (with and without metformin therapy). Therefore, in addition to BMI, serum lipid profile can be said to be another potent determinant of hs-CRP. This is consistent with a study performed by Verit,<sup>35</sup> to investigate hs-CRP levels in normo-insulinemic PCOS patients without metabolic syndrome. In opposition to this, Tarkun et al.,<sup>32</sup> did not find significant correlation between hs-CRP and any parameters of lipid profile in a study conducted in 37 Turkish women with PCOS.

## CONCLUSION

Metformin therapy for more than three months is associated with significant decrease of hs-CRP serum level and has beneficial effect on lipid profile in patients with PCOS. This is suggesting that metformin is associated with reduced cardiovascular risk in these patients.

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