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Original Article

# Analysis of CRP, Vitamin D and Metabolic Factors in Non-obese Patients with Polycystic Ovary Syndrome: a Cross Sectional Study in Imam Khomeini Hospital, Ahvaz

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## ABSTRACT

**Background and Objectives:** The polycystic ovary syndrome (PCOS) is one of the most common diseases diagnosed in women of childbearing age which is associated with increased risk of metabolic complications, including cardiovascular disease. Increasing C-reactive protein (CRP) as an inflammatory factor is common in these patients. In addition, vitamin D deficiency is quite common among females with PCOS. The aim of this study is to determine the relationship of CRP levels with vitamin D and metabolic factors in Non-obese Patients with PCOS.

**Materials and Methods:** This experimental study was done on 100 non-obese 20-40 years old females (BMI<30) who were diagnosed with PCOS. Based on CRP levels, the females are categorized in two groups (normal CRP<0.8 mg/dl). The serum levels of HOMA-IRC, FBS, HDL-C, LDL-CHL, Vitamin D and CRP of participants in the study were measured. Then, collected data was analyzed through the SPSS Software (version. 23). In all analysis, the p-value is presumed to be less than 0.05.

**Results:** The mean age of patients was 27.11±6.25. Patients in high CRP group, had significantly lower levels of HDL-C and higher Triglyceride (TG) compared to controls. In addition, the increase in CRP was associated with vitamin D deficiency. This was while no significant difference between the two groups of patients were observed in terms of insulin resistance.

**Conclusions:** The findings of present study suggest that higher CRP levels are positively correlated with vitamin D and HDL-C deficiency as well as an increased TG levels in non-obese females with PCOS. These findings have significant implications for the understanding of how vitamin D deficiency can contribute to inflammatory and metabolic responses in patients with PCOS. A future study could assess the long-term implications of vitamin D supplementation on inflammation and metabolic outcome of patients with PCOS.

**Keywords:** PCOS, Vitamin D, CRP, Inflammation, Metabolic Factors

## Introduction

The polycystic ovary syndrome is one of the most common endocrine diseases in females of reproductive age since it could affect 5 to 10 percent of the population and it is characterized by hyperandrogenism and anovulation (1). PCOS is detected when at least two of the following symptoms are diagnosed in a person: Irregular ovulation or anovulation, increases in androgenic hormones, or increase of ovarian size with at least 12 follicles (2). Some clinical symptoms of this syndrome are hirsutism, irregular menstrual cycles, and obesity (1).

Previous studies suggest that females with PCOS are at higher risk of cardiovascular diseases due to some occurring symptoms of metabolic syndrome such as abdominal obesity, insulin resistance, dyslipidemia and atherosclerosis (3). These studies report higher prevalence of metabolic syndrome in females with PCOS (4). In addition, 50 to 80 percent

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of these people show insulin resistance (5). The insulin resistance causes increments in the glucose level which consequently increases insulin and LH hormones. These events increase the amount of androgen hormones and the end result is PCOS (6).

One of the independent indicators of cardio-vascular diseases is C-reactive protein (CRP), which indicates the inflammatory status of the body (7). Some studies have reported the increase of CRP in females with PCOS (8). The high-sensitivity tests were conducted and CRP levels of less than 1mg/dl, 1-3 mg/dl and more than 3mg/dl were reported as indicating low, medium and high risk of cardiovascular disease respectively (1).

Vitamin D is one of the fat-soluble vitamins, the deficiency of which has turned into a health problem in the world. The reason might be the low exposure to direct sunlight and few nutritional sources with vitamin D (9). Most of existing evidence suggest that vitamin D deficiency plays a significant role in pathogenesis of metabolic syndrome in females with PCOS because vitamin D regulates 3 percent of genes recipients in human genome (3,10). In addition, the studies suggest that vitamin D deficiency could negatively affect LDL-C metabolism (9). Most of these studies suggest that there is an independent and significant association between serum concentration of 25-hydroxy vitamin D and serum level of APO-A and HDL-C (11).

This this study aimed to determine the relationship of CRP levels with vitamin D and metabolic factors in Non-obese Patients with PCOS.

## Materials and Methods

This experimental study was conducted on 100 females with PCOS who had visited Imam Khomeini Hospital (Ahvaz, Iran). The polycystic ovary syndrome is characterized by irregular menstruation such as oligomenorrhea (less than 9 times per annum menstruations), or Amenorrhea (lack of menstruation for three months or more) and clinical symptoms of hyperandrogenism (i.e. hirsutism, acne, and male pattern baldness). The exclusion criteria for the present study are obesity, non-classical congenital adrenal hyperplasia, thyroid dysfunction, androgen-secreting tumors, Cushing's syndrome, hyperprolactinemia, smoking, taking drugs for regulating blood sugar, atorvastatin, aspirin, contraceptive hormones or taking any medications two months before the start of sampling. All of the patients were thoroughly informed of this study by a written consents. All participants were in the age range of 20 to 40 years.

The anthropometric parameters of the participants (height, weight and waist) were measured in standard conditions. The patient weight were measured by scales with 100g accuracy, while they were wearing light clothes. In addition, patients' height were measured through a stadiometer with 0.5cm accuracy. Finally, body mass index was calculated through its distinct equation (i.e. weight divided by squared height). Also the waist circumference was measured from the small area between the last gear and spur.

In order to conduct biochemical tests, the fasting blood sample of patients were taken during follicular phase of the menstruation (between third and fifth day). Then, centrifusion was done and separated serum was stored in -20°C up to the time of test. For all patients, serum concentrations of blood sugar, insulin, high-sensitivity CRP, triglyceride, cholesterol, HDL, LDL and 25 (OH) vitamin D3 were measured. Total cholesterol, Triglyceride, HDL and LDL measurements were made using colorimetric method with a commercial kit with an automatic analyzer. Plasma glucose level was estimated by GOD-PAP enzymatic colorimetric method. Determination of CRP by high sensitive immunoassay for measuring the human CRP which is a two-step sandwich Elisa technique was used with a commercial kit.

The serum concentration of 25 (OH) vitamin D3 metabolites were measured through radioimmu-noassay (DRG System, Marburg: Germany). The measurement of serum insulin was carried out through IRMA (Biosource Europe, Nivelles: Belgium). The serum levels of sugar, cholesterol, triglyceride, LDL, and HDL were measured through standard methods (Sinagen, Tehran: Iran). In order to evaluate the CRP test with high sensitivity, the Architect C16000 (Abbot) was used. In addition, insulin resistance was determined through the haemeostatic model assessment (HOMA-IR).

HOMA-IR=Fasting insulin (mlU/mL)*fasting glucose (mg/dL)/405(12)

Finally, the patients were divided into two groups based on CRP levels (in this study, the cutoff point for CRP level was considered 3mg/dl) and levels of metabolic factors and vitamin D were compared by the Mann-Whitney U test. The data normality was evaluated by komogrov smirnov test. Moreover the descriptive results are shown as mean± S.d. All statistical analyses were done through the SPSS Software (version 23). The significance was presumed less than 0.05.

## Results

The mean age of participants in the study is 27.11±6.25 years. The results also suggested that 46 patients were in the BMI range of 20 and 24.9 kg/m$^2$ and the remaining 54 individuals were in BMI range of 25 and 29.9 kg/m$^2$. Among the patients participating in this study, 20.4 percent had normal

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CRP level and 79.5 percent of people had abnormal CRP level.

Based on measurements of fasting blood sugar, 79.5 percent of patients were in normal range (less than 100mg per deciliter), 13.6 percent of patients had disturbed levels of blood sugar and 6.8 percent of patients were suspected of diabetes. In addition, insulin resistance of patients in both groups did not show significant difference (p=0.12). In addition, both groups did not show significant difference in BMI, (CHOL), and LDL levels (p=0.79).

The mean TG levels in the group with normal CRP was 100.56±44.03 mg/dl while mean TG for the group with abnormal CRP was 144.97±121.64mg/dl. These results were significantly different between the two groups (p=0.012). In addition, the levels of vitamin D for the group with normal CRP and the group with abnormal CRP were 20.87±12.29 mg/dl and 14.87±9.51 mg/dl respectively. The difference is statistically significant (p=0.014).

**Table1.** Participant's characteristics

| General characteristics of patients | Normal CRP mean±sd | Abnormal CRP mean±sd |
|---|---|---|
| Weight (kg) | 65.85±9.94 | 66.95±10.21 |
| Hight (cm) | 161±0.090 | 165±0.255 |
| Age (Year) | 25.6±5.093 | 27.64±6.44 |
| Waist circumference(cm) | 94.7±1.2 | 110.4±20 |

RP NORMAL is less than 3mg/dl in plasma and CRP ABNORMAL is more than 3mg/dl.

**Table 2.** Means and standard deviations of dependent variables in both group

| Dependent variables | Crpnoramal mean±sd | Crp abnormal mean±sd | P value |
|---|---|---|---|
| serum 25(OH)D" (ng/ml) | 20.87±12.292 | 14.78±9.519 | 0.014(a) |
| LDL (mg/dl) | 91.61±28.193 | 90.36±23.602 | 0.79 |
| Cholestrol(mg/dl) | 162.06±33.08 | 163.47±27.295 | 0.65 |
| TG (mg/dl) | 100.56±44.038 | 144.97±121.644 | 0.046(a) |
| HDL (mg/dl) | 48.89±5.698 | 44.97±9.745 | 0.012(a) |
| FBS (mg/dl) | 96.72±16.764 | 92.46±16.541 | 0.21 |
| HOMA-IR | 6.65±7.13 | 4.37±5.02 | 0.12 |
| BMI (kg/m2) | 24.8±3.435 | 25.2±3.450 | 0.62 |

a) Significant difference (Mann-Whitney U) between crp normal and abnormal p-valu<0.05
CRP NORMAL is less than 3mg/dl in plasma and CRP ABNORMAL is more than 3mg/dl.

## Discussion

In this study, non-obese people with PCOS were categorized into two groups based on their CRP levels. Then, metabolic factors and vitamin D level of these two groups were compared.

The blood sugar analysis suggested that only 6.8 percent of patients had increased blood sugar while insulin resistance was diagnosed for 59.1 percent of the patients. The studies conducted by Galluzo *et al* and Legro *et al* have reported insulin resistance in patients with PCOS (13, 14).

The results of the current study suggested that levels of HDL-C and TG in patients with increased CRP Is significantly lower and higher than the other patients, respectively. These factors are significant risk factors for development of cardiovascular diseases. Gunning MN, *et al* (2017) and Dahlgren E, *et al* (2000) (15, 16) also reported abnormal levels of TG and HDL-C in patients with PCOS. These findings justify the high prevalence of cardiovascular diseases in patients with PCOS which is supported by other studies (16, 17).

In addition, levels of vitamin D for the group with and without normal CRP were 20.87±12.29 and 14.78±9.51 respectively. There were statistically significant difference between the two groups (p=0.014). These finding is in accordance with the results of Ngo *et al* (2011) and Holick, M, F & Chen, T, C (2008) (9, 17). Vitamin D and its metabolites reduce the inflammatory status and inflammatory factors of the body and this is done through

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phosphorylation of p38MAPK. However, changes in expression of MAPK phosphatase-1 does not happen. In addition, vitamin D reduces the amount of cytokines produced through NF-KB pathway but fixes mRNA of interleukin-8 so as to create an anti-inflammatory condition in the body (18). In addition, dose-dependent vitamin D inhibits monocytes from expression of TNF-alpha and 6IL (19). This is while previous studies suggest that increases in alpha-TNF is associated with insulin resistance (20). In addition, it has recently been proved that Monocyte chemotactic protein 1 (MCP-1) disrupts sensitivity of fat cells to insulin (21). This is while insulin resistance plays a critical pathogenic role in development of inflammatory diseases as well as cardiovascular disorders. In addition, numerous studies suggest that insulin resistance leads to increased TG and reduction of HDL (22,23). The role of inflammation in development of PCOS has drawn the attention of many researchers. Today, it is thoroughly suggested that as a PCOS-specific characteristic, hyperandrogenism is highly correlated with inflammation in patients with PCOS (24).

Conclusion

In general, the findings of present study suggest that reduced level of vitamin D contributes to an inflammatory condition. The inflammation might change metabolic and androgenic factors. These changes may lead to PCOS development and exacerbation. In addition, one may presume that, increased risk of cardiovascular and metabolic diseases in patients with PCOS is associated with vitamin D deficiency. However, proving the correlation requires further studies with bigger sample size and considering more inflammatory factor in patient. Due to the available result and prevalence of vitamin D deficiency in society, supplementation of vitamin D in these patients recommended.

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