Possible Effect of vitamin D3 on Follicular Maturation in Polycyctic Ovarian Syndrome (PCOS) Women

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Abstract

Polycystic ovarian syndrome (PCOS) is the most common reproductive age endocrine condition in women. Most likely, one of the major problems of PCOS patients are vitamin D3 deficiency. Therefore, investigation of the association between vitamin D3 deficiency and ovulation in PCOS women patients might help to explore the possible relationship between them. Sixty-six patients were recruited from a private clinic in Karbala city / Al-Hindiya district, Iraq. The patients were divided into two groups (33 patients each), the first group treated with metformin 850 mg, b.i.d, and placebo. The second group treated with metformin 850 mg, b.i.d and vitamin D3 oral supplementation 5000 IU/day for 3 months. Ultrasonography was performed monthly on day 13 to assess the follicular size. D3 blood level was measured at the end of the 3 months. The present study demonstrated that daily D3 5000IU in PCOS women with deficient D3 whom already on scheduled metformin 850 mg b.i.d for 3 months significantly ($p<0.05$) increased the mid-cycle follicular size by one 3rd in comparison to placebo group. The important finding was that vitamin D3 might enhance follicular maturation in PCOS patients.

Keywords: *D3 supplementation, ovulation, polycystic ovarian syndrome (PCOS).*

Introduction

The most widely diagnosed female endocrine disease is polycystic ovarian syndrome (PCOS), which is almost 5-10% among females in generative age [1]. PCOS has at minimum two measures of 3: raised androgenic hormones, unbalanced or absent ovulation and protracted ovaries with additional than 12 follicles each [2]. In addition, PCOS is linked to a variation of cardiovascular danger causes such as insulin resistance (IR), obesity, decreased glucose tolerance, elevation blood pressure, and type 2 diabetes [3]. Females with PCOS commonly consume metabolic illnesses and IR, which may be related with the unusual vitamin D metabolism [4]. Vitamin D3 affects the metabolism of glucose and insulin and is essential in T2DM [5]. The mechanisms through which vitamin D3 levels might have an association with an IR or T2DM are not yet clear. According to studies, it might be related to: first, low concentrations of vitamin D3 might lead to increase levels of serum parathyroid hormone and by the way altering glucose and reducing the susceptibility to insulin [6]. In addition, high than 300 genes counting the genes related with glucose metabolism are regulated by vitamin D3 and the vitamin D3 receptor (VDR) [7]. Based on the above-mentioned associations between vitamin D3 besides insulin, or glucose, numerous earlier studies explored vitamin D function in PCOS [8]. However, there was no strong consensus as regards the significance of serum vitamin D3 levels in PCOS and non- PCOS patients, a reverse association was found in PCOS patients with serum 25-hydroxyvitamin D3 levels with metabolism disturbances [9]. Moreover, previous studies have shown that PCOS women also have vitamin D deficiency [10]. Furthermore, several studies have shown the improvement of several PCOS laboratory and clinical findings by supplementation of vitamin D3 among the vitamin D3 deficiencies PCOS women [11]. However, in general and according to our knowledge, there has been no significant impact regarding the relationship between PCOS, IR and vitamin D3 deficiency. The aim of this study was to investigate the relationship between

vitamin D3 and mid-cycle ovarian follicle maturation in PCOS patients with vitamin D3 deficiency.

Materials and Methods

Study design

The present study is a clinic based prospective observational study conducted on 66 patients with PCOS, both suspected and already diagnosed who attending to a private clinic in Karbala city / Al-Hindyya district, Karbala province, Iraq, from 13th of January 2019 to 4th of July 2019.

Criteria for selecting patients

•All newly suspected and diagnosed cases of PCOS.

•Aged 20-35 years.

• History of infertility, PCOS with low D3 blood level (<10ng/ml).

Exclusion criteria included:

•Any diagnosed case of PCOS who was on and had history of taking vitamin D3 and calcium supplement within period of one year.

•Diagnosed cases of PCOS who was under treatment and recovered with treatment (medical or surgical).

•Patients who were not willing to take part in our study.

The patients were distributed into two groups:

1. Group 1: (33 patients) treated with metformin 850 mg, b.i.d, and placebo.

2. Group 2: (33 patients) treated with metformin 850 mg, b.i.d and vitamin D3 oral supplementation 5000 IU/day for 3 months (single blind technique).

Patients follow up parameters included mid-cycle follicular size was assessed monthly on day 13 using Ultrasonography. 2-D3 blood level was measured before and at the end of the 3 months.

Statistical Analysis

SPSS version 20 (SPSS, IBM Company, Chicago, IL 60606, USA) was used to conduct statistical analysis. Consistent variables (means ± SD) have been presented. The means between two groups is compiled with independent t-test samples. The t-test paired has been used to compare readership methods. A *p-value* of up to 0.05 was considered significant. Data were subjected to one-way ANOVA testing and multiple comparisons Dunnett testing.

Ethical Consideration : The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Verbal consents of the patients were taken after explaining the purpose of the study to the patients. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee.

Results

3.1 Effects of metformin and placebo on D3 serum level in PCOS patients. There was no significant (p>0.05) changes in D3 blood level between control group (before metformin, 850mg + placebo) and a group treated with the same regime for 3 months.

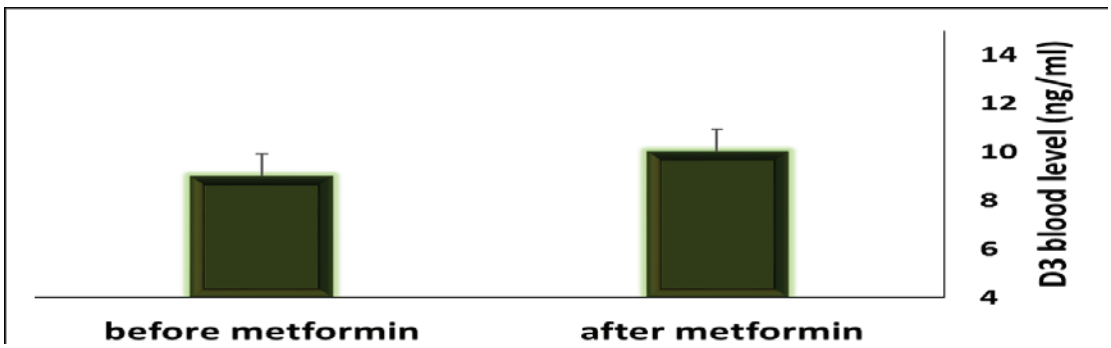

Figure 1. The effect of Metformin 850 mg b.i.d and placebo on D3 blood level (ng/ml) for 3 months P > 0.05. Data is stated as the mean changes in D3 level (± SEM) (n =33 in each group). In addition, One-way ANOVA test stated Statistical significance following correction by Dunnett's for multiple comparison.

3.2 Effect of metformin and D3 on D3 serum level in PCOS patients. There was a significant ($p<0.05$) increase in D3 blood level after oral supplementation of metformin, 850 mg + vitamin D3 5000 IU for 3 months in comparison to control group.

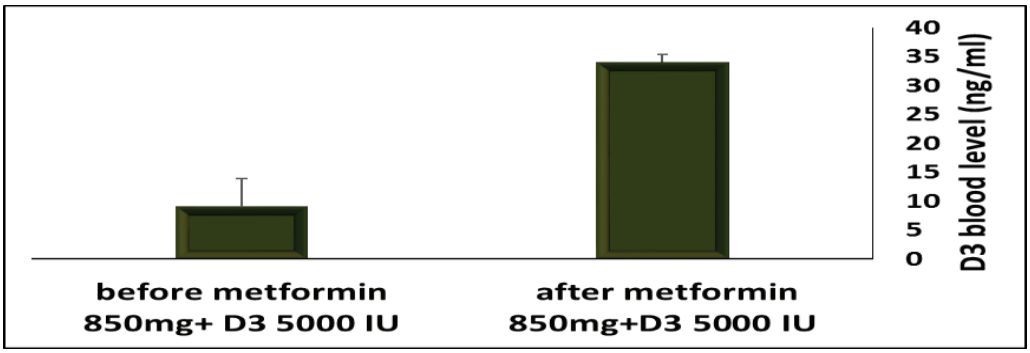

Figure. 2 The effect of Metformin 850 mg b.i.d and D3, 5000IU on D3 blood level (ng/ml) for 3 months. P < 0.05. Data is stated as the mean changes in D3 level (± SEM) (n =33 in each group). In addition, One-way ANOVA test stated Statistical significance following correction by Dunnett's for multiple comparison.

3.3 Effect of metformin and placebo on mid-cycle follicular size in PCOS patients. There was no significant ($p>0.05$) changes in mid-cycle follicular size between control group (before metformin, 850 mg + placebo) and a group treated with the same regime for 3 months.

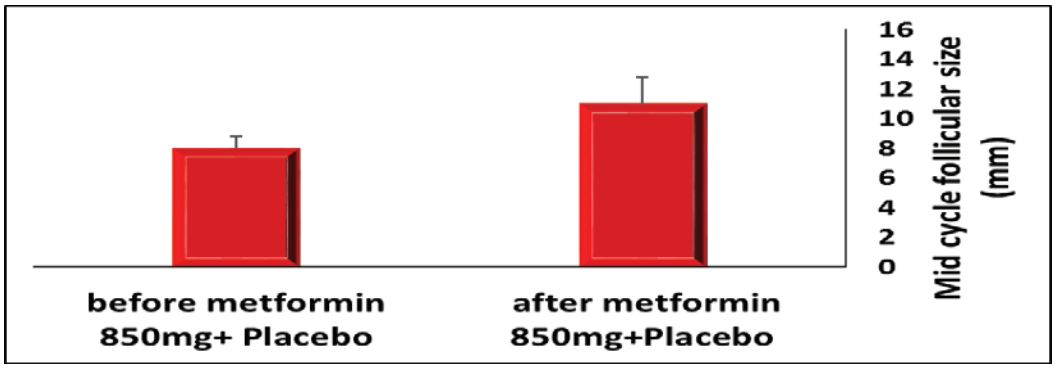

Figure. 3 The effect of Metformin 850 mg b.i.d and placebo on follicular size (mm) for 3 months. P > 0.05. Data is stated as the mean changes in follicular size (± SEM) (n =33 in each group). In addition, One-way ANOVA test stated Statistical significance after correction by Dunnett's for multiple comparison.

3.4 Effect of metformin and D3 on mid-cycle follicular size in PCOS patients. There was a significant ($p<0.05$) increase in mid-cycle follicular size after oral supplementation of metformin, 850 mg + vitamin D3 5000 IU for 3 months in comparison to control group.

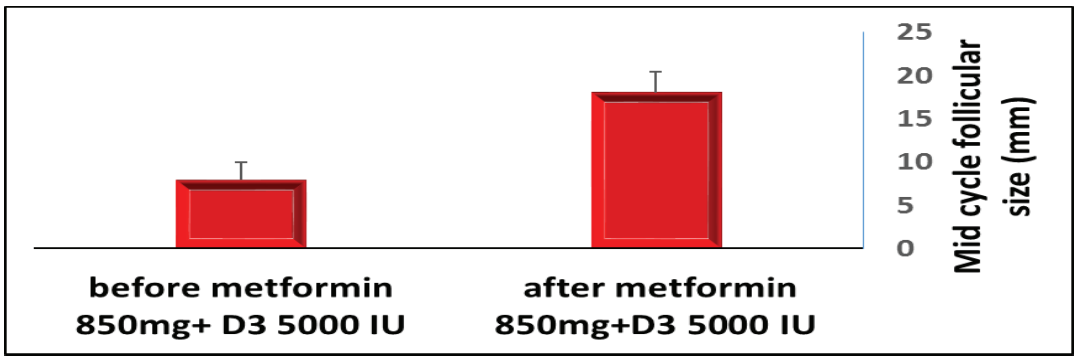

Figure. 4 The effect of Metformin 850 mg b.i.d and D3 5000IU on follicular size (mm) for 3 months. P < 0.05. Data is stated as the mean changes in follicular size (± SEM) (n =33 in each group In addition, One-way ANOVA test stated Statistical significance following correction by Dunnett's for multiple comparison.

3.5 Comparison between effect of metformin+ placebo and metformin+ vitamin D3 on serum D3 level in PCOS patients. There was a significant ($p<0.05$) increase in D3 blood level after oral supplementation of metformin, 850 mg + vitamin D3 5000 IU for 3 months in comparison to metformin 850mg + placebo group.

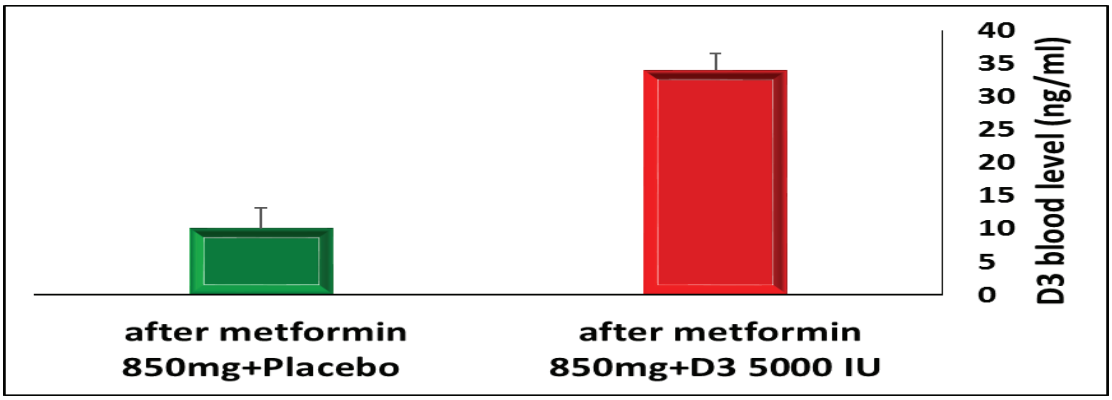

Figure. 5 The effect of Metformin 850mg b.i.d + placebo and D3 5000IU on D3 blood level (ng/ml) for 3 months. P < 0.05. Data is stated as the mean changes in D3 level (± SEM) (n =33 in each group. In addition, One-way ANOVA test stated Statistical significance after correction by Dunnett's for multiple comparison.

3.6 Comparison between effect of metformin+ placebo and metformin+ vitamin D3 on mid-cycle follicular size in PCOS patients. There was a significant ($p<0.05$) increase in mid-cycle follicular size after oral supplementation of metformin, 850 mg + vitamin D3 5000 IU for 3 months in comparison to metformin 850 mg + placebo group.

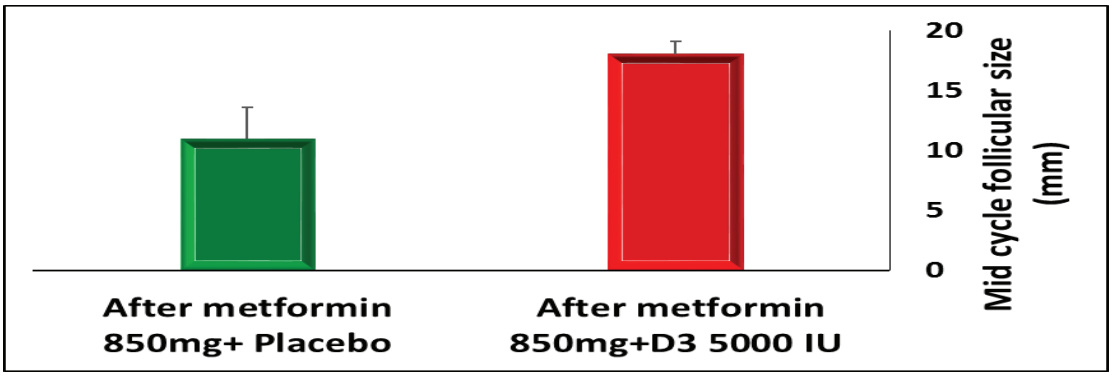

Figure. 6 The effect of Metformin 850mg b.i.d + placebo and D3 5000IU on follicular size (mm) for 3 months. P < 0.05. Data is stated as the mean changes in follicular size (± SEM) (n =33 in each group). In addition, One-way ANOVA test stated Statistical significance following correction by Dunnett's for multiple comparison.

Discussion

Vitamin D3 effect on ovarian role showed mostly in the medical studies of its consequence on obstetrical results, mostly in patients with ovarian illnesses looking for fertility management [11]. Presently, information are not reliable concerning the association between follicular liquid vitamin D3 focuses and gestation degrees, with optimistic, adverse, and unimportant [12] associations stated. However, vitamin D3 supplementation looks to be supportive to people's grief from obesity besides insulin resistance. Revisions in PCOS patients designated that vitamin D3 supplementation better follicular development, leading follicle creation, and gestation rates increase, and reinforced the recommencement and upkeep of menstrual sequences [13]. Pathophysiological contrivances by which vitamin D3 controls follicular development besides ovum eminence are quiet unclear because absence of sufficient and correct study replicas.

PCOS is the most common reproductive age endocrine condition in women [1]. One of the major problems of PCOS and related infertility patients are most likely vitamin D3 deficiency [2] However,

there is a continuing debate that if vitamin D3 levels correlate with the risk of PCOS, and whether the supplementation of vitamin D3 is effective therapy for PCOS and consequently infertility. Basically, this study was performed to assess the possible effects of vitamin D3 supplementation in PCOS patient with vitamin D3 deficiency on mid-cycle follicular size on the 13th of ovulation and subsequently on the infertility, as a major issue associated with PCOS, in general.

In the worldwide of reproduction, the consequence of vitamin D mainly exposed in tests with mice. Mice who are both lacking in vitamin D, or who absence the receptor of vitamin D, can confirm low development of the uterus besides inability to form usual developed follicles, subsequent in infertility. If gestation is occurred, the fetuses demonstration growth deficiency. Reproduction regularized in mice by supplementation of vitamin D3, not calcium only, suggesting that vitamin D character in woman reproduction is not connected to helping the absorption of calcium from the body [14]. In previous studies, the role of vitamin D is highlighted in female reproductive activities such as steroidogénesis, which may improve granulose cell proliferation, ovulation and follicular growth [15]. Parikh et al. [16] showed that vitamin D led to the production of a growth factors-binding protein 1 in human ovarian cells, including progesterone, estrogen, and insulin. Nevertheless, vitamin D deficiency in the growth of ovarian follicles and PCOS patients is normal in women with PCOS. Furthermore, vitamin D deficiency is still not entirely clear. Therefore, vitamin D3 effect on the ovarian follicular development of women with PCOS was investigated by the study in this field.

The present study depicted that daily supplementation of vitamin D3 5000 IU in PCOS women with deficient D3 blood level whom already on scheduled metformin 850mg b.i.d for 3 months significantly ($p<0.05$) increased the mid-cycle follicular size by one 3rd in comparison to placebo group.

This is in line with the Kotsa et al study [17], who showed the fact that the majority of PCOS women have a vitamin D and PTH-vitamin D axis abnormality. Thys-Jacobs et al demonstrated the follicular arrest and follicular production of Vitamin D deficiency that is strongly consistent with our findings [18].

Furthermore, an important previous study showed that vitamin D has promoted folliculogenesis and follicular growth in rats with PCOS through increased concentrations of estrogen and progesterone and regulation of the FSH and LH ratios [19]. These results are consistent with those of Kinuta et al [17]. Moreover, Nasim et al showed that vitamin D supplementation regulates the ratio of androgen hormones, increases the sensibility to insulin in rats that have PCOS, thereby stimulating dominant follicles to develop and ovulating matured follicles [20].

Overall, PCOS is the most common reason of an ovulatory infertility in women. The mechanism behind this issue is still unclear. In PCOS, ovarian composition firmly connected to the metabolic engagements detected in this illness; so, a valued result of vitamin D3 on the metabolic changes might interpret into a improved and reinstated ovarian physiology [21]. Maximum PCOS females are both obese or overweight, creation it problematic to organize that vitamin D3 lack subsidizes to the pathogenesis of PCOS self-sufficiently from raised body mass index [BMI]. Obesity may reduction circulating 25OH-D by misleading this lipophilic vitamin inside adipose tissue. So, the acceptable possessions of vitamin D3 on the metabolic changes in PCOS, composed with the rise in anti-inflammatory solvable receptor for progressive glycation yields force alter into an upgrading in ovarian composition. Supplementation of vitamin D3 therefore holds a possible of flattering a likely beneficial assistant for the dysfunction of ovulation and metabolic changes experiential in females with PCOS [22].

Conclusion

Obviously, the results from this study strongly showed that the vitamin D3 blood levels are related to the risk of immature follicular size in patients with PCOS. However, in the PCOS women, with and without calcium and vitamin D3 deficiency, it is very hard to find out the exact therapeutic impact of Vitamin D3 supplementation and its effect on the sex hormones, obesity, and IR to be the subject of further study.

Ethical Clearance: The Research Ethical Committee at scientific research by ethical approval of both MOH and MOHSER in Iraq

Conflict of Interest: None

Funding: Self-funding

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