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Effects of D3 supplementation on ovulation in polycyctic ovarian syndrome (PCOS) patients

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Abstract

Objectives: *To explore the relation between vitamin D3 and ovulation in PCOS patients with vitamin D3 deficiency.* ***Patients and Methods:*** *66 Patients were recruited from a private clinic in Karbala city / Al-Hindiya district. Criteria for selecting patients: aged 20-37 years, history of infertility, PCOS with low D3 blood level (<10ng/ml). The patients were divided into two groups (33 patients each), the first group treated with metformin 850mg, b.i.d, and placebo. The second group treated with metformin 850mg, 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. Data underwent one-way ANOVA testing and Dunnett's test for multiple comparisons.* ***Conclusion:*** *The important finding was that D3 might affect follicular maturation in PCOS patients.*

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

I. Introduction

Polycystic ovary syndrome (PCOS) is the most commonly diagnosed female endocrine disorder, with a prevalence rate of nearly 5–10% among women of reproductive age [1]. PCOS is characterized by elevated ovarian secretion of adrenal androgens, hyperandrogenic symptoms, including hirsutism, menstrual irregularity, acne and/or alopecia, as well as polycystic ovaries [2]. PCOS is defined by the appearance of at least two of the following criteria: increased androgenic hormones, irregular or absent ovulation, and enlarged ovaries comprising over 12 follicles each [3]. Moreover, PCOS is correlated with a variety of cardiovascular risk factors, such as insulin resistance (IR), obesity, impaired glucose tolerance, hypertension, type 2 diabetes (T2DM), and metabolic syndrome (MS) [4]. Women with PCOS usually suffer from metabolic disturbances and IR, which might be associated with vitamin D metabolism [5]. Vitamin D metabolism affects glucose and insulin metabolism and plays a significant

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role in T2DM [6,7]. The mechanisms by which serum vitamin D levels influence IR or T2DM are not yet clear, but previous studies found some important clues. First, low vitamin D concentration leads to an increased serum parathyroid hormone (PTH) level and elevated concentrations of PTH alter glucose metabolism and reduce insulin sensitivity [8,9]. Vitamin D may increase insulin receptor expression to improve insulin responsiveness in cells for glucose transport [10]. Further, vitamin D and the vitamin D receptor (VDR) regulate the expression of more than 300 genes, including the genes associated with glucose metabolism [11]. In view of the above correlations between vitamin D and insulin or glucose metabolism, several previous studies have examined the role of vitamin D in PCOS [12,13]. Although there is still no definite consensus on the significance of serum vitamin D levels in patients with PCOS and those without PCOS, an inverse correlation between serum 25OHD concentrations and metabolic disturbances was reported in PCOS patients [14]. Accordingly, previous studies revealed that women with PCOS frequently had associated vitamin D deficiency,2, [15]. Moreover, multiple studies have shown that vitamin D3 supplementation in vitamin D deficiency led to improvements in several laboratory and clinical parameters of PCOS [16,17]. However, another study failed to observe a positive influence of vitamin D3 supplementation on insulin-sensitivity in PCOS.3

1.1 Aims of the study

The aims of this study is to explore the relation between vitamin D3 and mid-cycle ovarian follicle maturation in PCOS patients with vitamin D3 deficiency.

II. Patients and Methods

The present study was clinic based prospective observational study and was conducted on patients of PCOS, both suspected and already diagnosed attending a private clinic in Karbala city / Al-Hindyya district from 18th of February 2019 to 7th of June 2019.

Basically 110 Patients were recruited from a private clinic in Karbala city / Al-Hindiya district.

2.1 Criteria for selecting patients

Inclusion criteria.

- All newly suspected and diagnosed cases of PCOS.
- Aged 20-37 years.
- History of infertility, PCOS with low D3 blood level (<10ng/ml).

Exclusion criteria

- Any diagnosed case of PCOS who was on and had history of taking vitamin D and calcium supplement within period of one year.
- Diagnosed cases of PCOS who was under treatment and recovered with treatment (medical and surgical).
- Patients who were not willing to take part in the study.

The patients were divided into two groups:

1- **Group 1:** (55 patients) treated with metformin 850mg, b.i.d, and placebo.

2- **Group 2:** (55 patients) treated with metformin 850mg, b.i.d and vitamin D3 oral supplementation 5000 IU/day for 3 months (single blind technique).

2.2 Patients follow up parameters

1- Mid-cycle follicular size was assessed monthly on day 13 using Ultrasonography.

2- D3 serum level was measured before and at the end of the 3 months.

2.3 Statistical analysis

Statistical analysis was carried out using SPSS version 20. Continuous variables were presented as (Means ± SD). Independent samples t-test was used to compare means between two groups. Paired t-test was used to compare means for paired reading. A p-value of ≤ 0.05 was considered as significant. Data underwent one-way ANOVA testing and Dunnett's test for multiple comparisons.

III. Results

3.1 Effects of metformin and placebo on D3 serum level in PCOS patients.

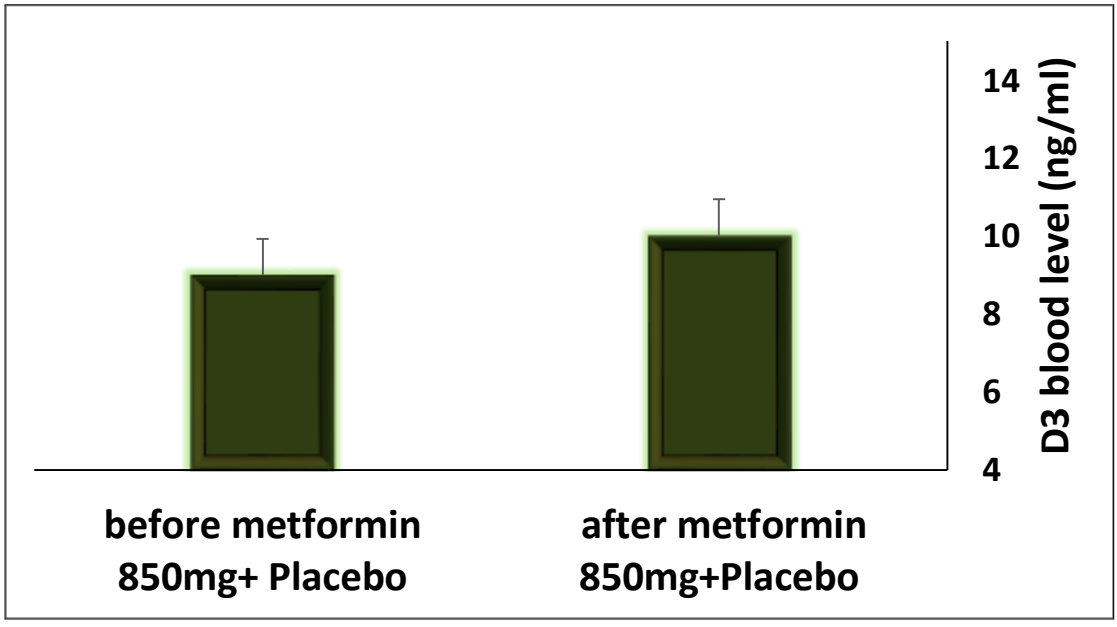
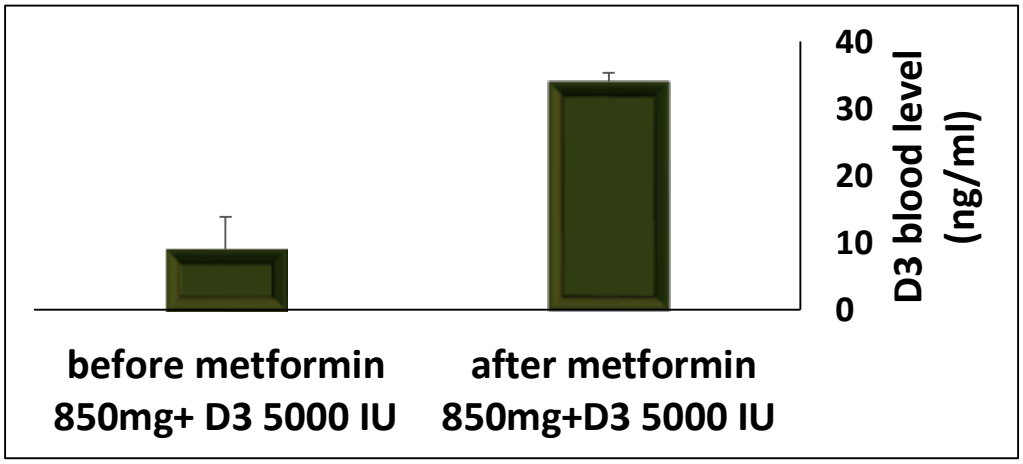


Figure 1. The effect of Metformin 850mg b.i.d and placebo on D3 blood level (ng/ml) for 3 months $P > 0.05$. Data is expressed as the mean change in D3 level (± SEM) (n =55 in each group). Statistical significance was determined by one-way ANOVA testing followed by Dunnett correction for multiple comparisons.

3.2 Effect of metformin and D3 on D3 serum level in PCOS patients.

Figure.2 The effect of Metformin 850mg b.i.d and D3, 5000IU on D3 blood level (ng/ml) for 3 months. *P < 0.05*. Data is expressed as the mean change in D3 level (± SEM) (n =55 in each group). Statistical significance was determined by one-way ANOVA testing followed by Dunnett correction for multiple comparisons.



3.3 Effect of metformin and placebo on mid-cycle follicular size in PCOS patients.

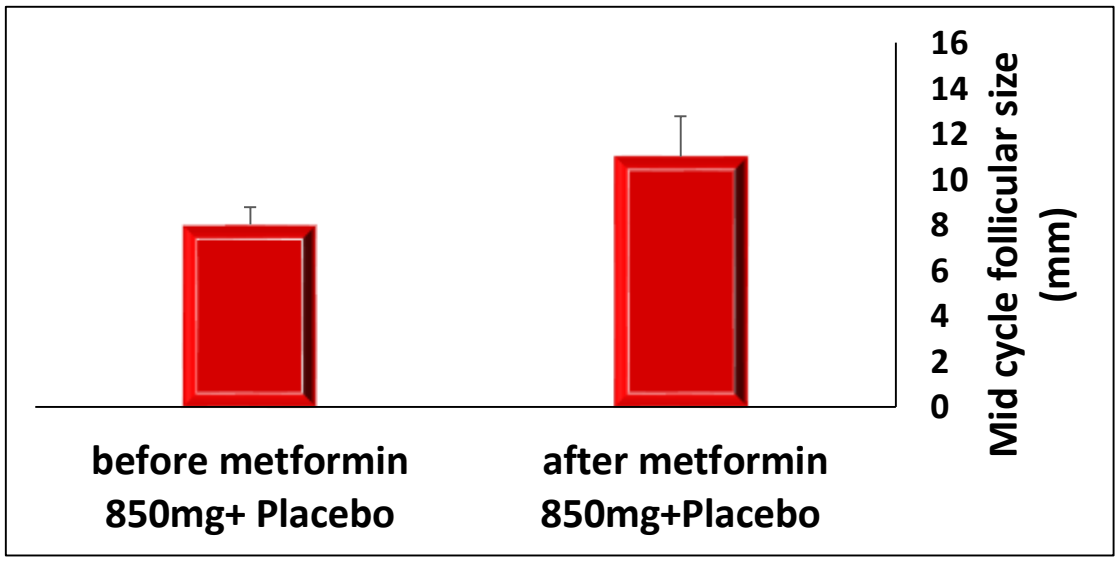


Figure.3 The effect of Metformin 850mg b.i.d and placebo on follicular size (mm) for 3 months. *P > 0.05*. Data is expressed as the mean change in follicular size (± SEM) (n =55 in each group). Statistical significance was determined by one-way ANOVA testing followed by Dunnett correction for multiple comparisons.

3.4 Effect of metformin and D3 on mid-cycle follicular size in PCOS patients.

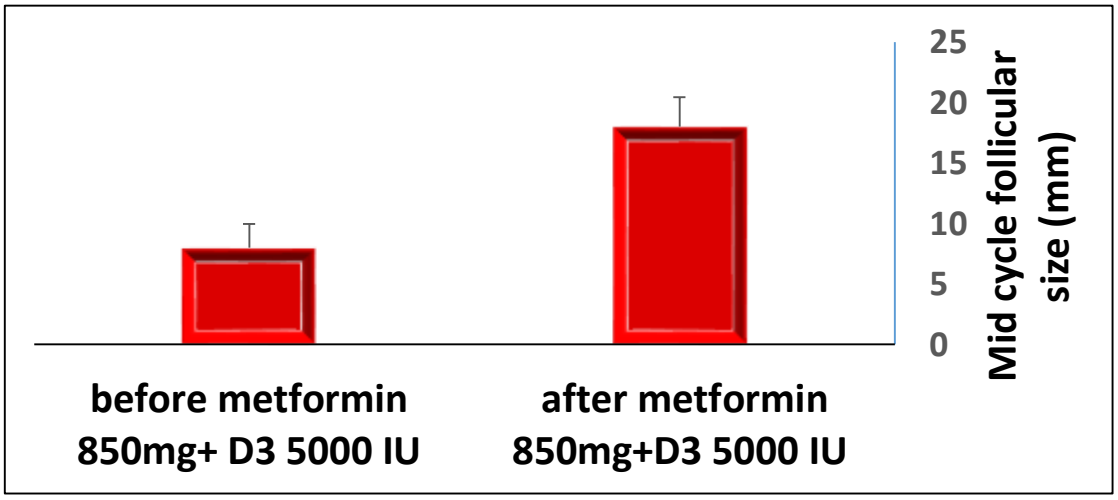


Figure.4 The effect of Metformin 850mg b.i.d and D3 5000IU on follicular size (mm) for 3 months. *P < 0.05*. Data is expressed as the mean change in follicular size (± SEM) (n =55 in each group). Statistical significance was determined by one-way ANOVA testing followed by Dunnett correction for multiple comparisons.

3.5 Comparison between effect of metformin+ placebo and metformin+ vitamin D3 on serum D3 level in PCOS patients.

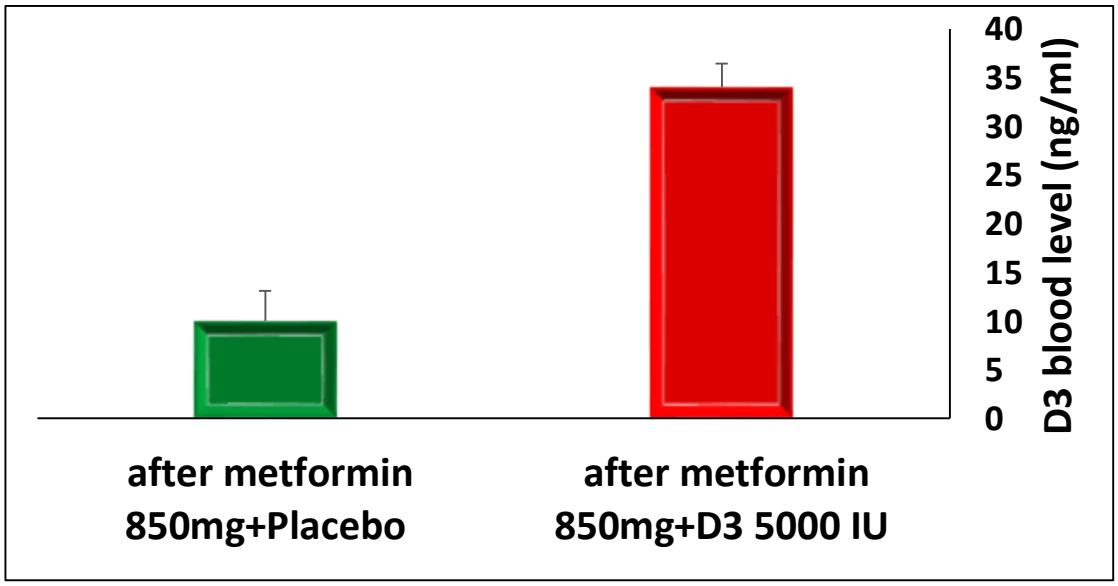


Figure.5 The effect of Metformin 850mg b.i.d + placebo and D3 5000IU on D3 blood level (ng/ml) for 3 months. *P < 0.05*. Data is expressed as the mean change in D3 level (± SEM) (n =55 in each group). Statistical significance was determined by one-way ANOVA testing followed by Dunnett correction for multiple comparisons.

3.6 Comparison between effect of metformin+ placebo and metformin+ vitamin D3 on mid-cycle follicular size in PCOS patients.

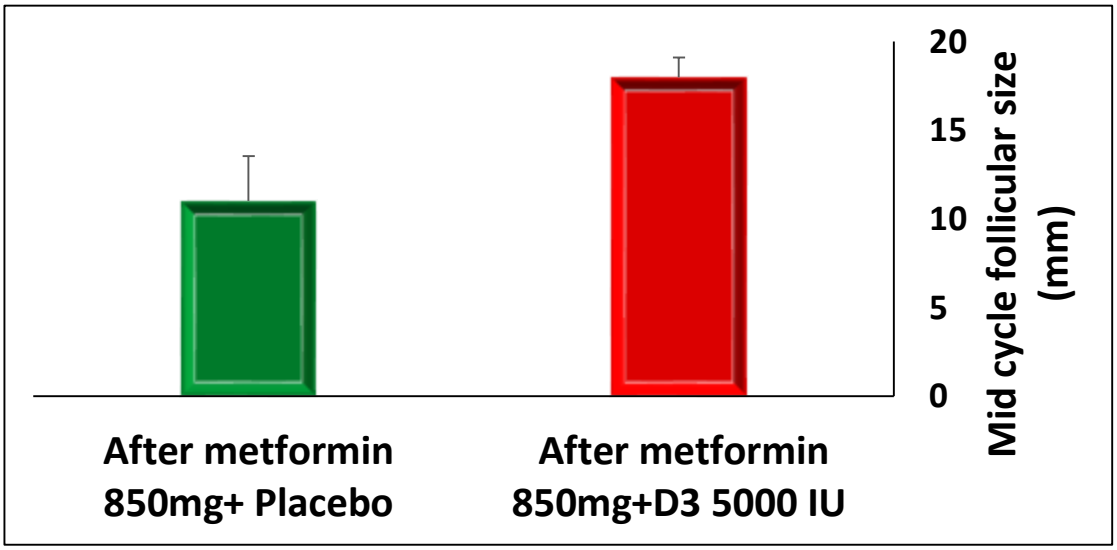


Figure.6 The effect of Metformin 850mg b.i.d + placebo and D3 5000IU on follicular size (mm) for 3 months. *P < 0.05*. Data is expressed as the mean change in follicular size (± SEM) (n =55 in each group). Statistical significance was determined by one-way ANOVA testing followed by Dunnett correction for multiple comparisons.

IV. Discussion

PCOS is the most frequent endocrine disorder among women of reproductive age [1]. Vitamin D deficiency is a general problem in PCOS patients [3] and debate continues regarding whether vitamin D concentrations are correlated with PCOS risk and whether vitamin D supplementation is an effective therapy for PCOS. Consequently, we examined the association between the serum level of vitamin D3 and PCOS as well as the therapeutic effect of vitamin D3 supplementation in PCOS patients on the mid-cycle follicular size at day 13 of ovulation.

The vitamin D receptor is expressed in the ovary, endometrium, placenta and testis, suggesting that vitamin D plays a critical role in these tissues [18]. Previous studies have highlighted the role of vitamin D in female reproductive functions such as steroidogenesis, which can enhance granulosa cell proliferation, oocyte activation, ovulation, and follicular development [19,20,21]. Parikh et al [22] demonstrated that vitamin D induced the production of progesterone, estrogen, and insulin-like growth factor-binding protein 1 in human ovarian cells. However, vitamin D deficiency is commonly found in women with PCOS, but the role of vitamin D deficiency in ovarian follicles development and patients with PCOS is not yet entirely clear. Therefore, the aim of the current study was to investigate the effect of vitamin D on ovarian follicular development in women with PCOS.

The present study demonstrated that daily D3 5000IU in PCOS women with deficient D3 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.

These results are in agreement with the study of Kotsa et al which indicated that the majority of women with PCOS had vitamin D deficiency and abnormalities in the PTH-vitamin D axis [23]. Thys-Jacobs et al revealed that vitamin D deficiency induced follicular arrest and impaired follicular development which is highly consistent with our results [24].

Moreover, cumulative studies found that vitamin D induced follicular development by antiapoptotic functions and the regulation of Bcl-family and Bax [25,26]. Our results were consistent with those of Kinuta et al demonstrating that vitamin D promoted folliculogenesis and follicular development in rats with PCOS by increasing estrogen and progesterone concentrations and regulating the FSH and LH ratio [25]. In addition, a study by Nasim B. et al demonstrated that Vitamin D supplementation in rats with PCOS regularized the androgen hormones ratio, increased insulin sensitivity, and thereby stimulated the development of the dominant follicles and the ovulation of matured follicles [27].

V. Conclusion

In conclusion, our results strongly suggest that the serum concentration of vitamin D3 is associated with the risk of immature follicular size in PCOS patients. However, we failed to detect the exact therapeutic effect of vitamin D3 supplementation in PCOS, with and without calcium, and its effect on sex hormones which will be a topic of further study.

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