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Original Research Article

A study on effect of vitamin d supplementation in vitamin D deficient females with polycystic ovarian syndrome

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ABSTRACT

Background: Polycystic ovarian syndrome is one of the most common metabolic and endocrine disorders among women, whereas vitamin D is a steroid with hormone like activity and also considered as a missing link between insulin resistance and PCOS due to its underlying mechanism of action in reducing insulin resistance thereby altering pathogenesis behind PCOS symptoms.
Methods: A prospective cohort comparative observational study was carried out from July 2019 to December 2020 in 96 vitamin D deficient females with PCOS (polycystic ovarian-syndrome). All females were randomly recruited under group A and B with equal proportion of 1:1, where group A were given metformin (500 mg twice daily) only and group B were given metformin (500 mg twice daily) plus vitamin D 60000 IU weekly for 24 weeks. Baseline clinical, hormonal, metabolic, sonographic parameters were compared before and after treatment.
Results: Significant improvement was seen in various parameters in both the groups, like oligomenorrhoea improved in 41.67% individuals. FG score improved from mean of 10.28±2.02 in group B to 8.44±2.23 with $p<0.0001$. Acne improved in both groups equally in 22.92%. Polycystic ovary pattern improved in 14.58% individuals of group B with $p<0.0001$. Serum total testosterone improved in 16.71% in group A and in 22.92% in group B. HOMA-IR was also reduced in both groups effectively and was statistically significant with $p=0.017$ in group A and $p=0.001$ in group B.
Conclusions: Remarkable improvement was seen in clinical, hormonal, metabolic and sonographic parameters in group B and noteworthy reduction in HOMA-IR, BP and triglyceride values was also seen. Hence, supplementation of vitamin D is highly effective in improving PCOS and preventing future consequences as well.

Keywords: PCOS, Polycystic ovarian syndrome, Vitamin D deficiency

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age, with a prevalence up to 10%.[1] It is characterized by ovulatory dysfunction (oligomenorrhoea or anovulation), hyperandrogenism and/or polycystic ovarian morphology.[2]

PCOS women have higher risks of endometrial cancer, cardiovascular disease, dyslipidemia and type 2 diabetes mellitus.[3,4] This draws attention to the need of early diagnosis and management of PCOS in adolescent girls.

Prevalence of vitamin D deficiency, is high as estimated in different studies worldwide.[5-8] Whereas, in INDIA, community-based studies done previously have reported a prevalence ranging from 50% to 94%, which is very high.[9-16] Furthermore, in women with PCOS, vitamin D deficiency was observed in 70.3% women, 20.3% were vitamin D insufficient and only 9.4% were vitamin D sufficient.[17]

Vitamin D is a steroid with hormone like activity that regulates function of over 300 genes and hence its supplementation has been extensively studied in various disease management worldwide.[18] Vitamin D stimulates

the expression of insulin receptors and signalling transduction, resulting translocation of $GLUT_4$ (glucose transporter) to the membrane and glucose transports in peripheral tissues. Vitamin D causes activation of peroxisome proliferator-activated receptor (PPAR-δ), a transcription factor implicated in the regulation of fatty acid metabolism.[19]

Thus, present study was carried out to see its effect after supplementation in PCOS vitamin D deficient females.

Aims and objectives

To observe the effect of 24 weeks of vitamin D supplementation, on the clinical features, hormonal, metabolic and sonographic parameters in vitamin D deficient females with PCOS.

METHODS

For a prospective cohort comparative observational study, 96 vitamin D deficient women aged between 15-35 years, presenting with PCOS (according to Rotterdam criteria) and vitamin D deficiency level ≤20 ng/ml, were serially recruited from general OPD of Tirath Ram Shah Charitable Hospital, New Delhi, during a period from July 2019 to December 2020.

Inclusion criteria

All willing, vitamin D deficient women with polycystic ovarian syndrome diagnosed in accordance with 'Rotterdam consensus conference criteria 2003'.

Exclusion criteria

Pregnant, postpartum, or breastfeeding women. History of cigarette smoking or alcohol consumption. Current or previous use (within 3 months) of oral contraceptives, antidiabetics, statins, glucocorticoids, antiepileptics, insulin sensitizers, vitamin D or intake of any other drugs known to affect endocrine parameters, carbohydrate metabolism, or calciotropic hormone concentrations. Other hormonal dysfunctions: hypothalamic, pituitary, thyroid, adrenal causes where clinical signs may mimic PCOS. Neoplasms (ex. androgen secreting tumours). Unstable mental illness. Known case of diabetes mellitus, thyroid disorders, malabsorption, liver disease, renal disease, epilepsy, cardiovascular disease.

Firstly, all the patients were subjected to history taking, clinical examination- general physical examination, vitals, systemic examination was done.

A detailed clinical history with specific reference to age, menstrual pattern, weight gain, excessive hair growth or loss, acne, smoking and alcohol habits was taken.

Then they were advised to undergo baseline investigations (fasting serum glucose, two-hour blood glucose after 75 gm oral glucose load taken after fasting state (mg/dl), Fasting serum insulin and 2 hours of postprandial insulin after 75 gm of glucose, serum LH, FSH and free testosterone, serum TSH, lipid profile, serum vitamin D) and ultrasound pelvis.

Cut off used in our laboratory for serum vitamin D were vitamin D deficiency- <10 ng/ml, vitamin D insufficiency- 10-20 ng/ml, vitamin D sufficiency- >20ng/ml.

$$\text{HOMA IR} = \frac{\text{fasting serum Insulin (mIU/l)} \times \text{Fasting BS (mg/dl)}}{405}$$

Cut off used for HOMA-IR: >2.5.

So, patients were alternately divided into 2 groups (group A and group B). Group A received metformin 500 mg twice daily and group B received metformin 500 mg twice daily plus vitamin D in a dose of 60,000 IU/week orally for 24 weeks. Allocation ratio was 1:1. Clinical features, anthropometric measurements and relevant investigations were noted at start of therapy as baseline and patients were called for follow up after 24 weeks of treatment.

After 24 weeks of therapy, clinical features, anthropometric measurements were again noted down and metabolic, hormonal, sonographic parameters were repeated and compared with baseline parameters.

The side effects experienced in each group were recorded. Finally, efficacy of the therapy was observed.

Statistical analysis

The presentation of the categorical variables was done in the form of number and percentage (%). On the other hand, the presentation of the continuous variables was done as mean±SD and median values. The following statistical tests were applied for the results.

The comparison of the variables which were quantitative in nature were analysed using independent t test. Paired t test was used for comparison across follow up. The comparison of the variables which were qualitative in nature were analysed using Chi square test and if any cell had expected frequency <5 then Fisher's exact test was used.

Statistical analysis

The data entry was done in the Microsoft Excel spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software version 21.0. For statistical significance, p value of less than 0.05 was considered as significant.

RESULTS

Present study was carried out in 96 patients with PCOS and vitamin D deficiency. The results and observations of the

pre therapy (baseline) and after therapy (met- metformin 500 mg twice daily in group A and metformin 500 mg twice daily plus vitamin D 60000 IU in group B) investigations that we sent for assessment are as follows. Baseline demographic data were comparable in both the groups. Majority of the patients were in the age group of 16-25 years (60.42%). Table 1 explains that out of total, 69.79% of patients who presented with oligomenorrhea (66.67% in group A and 72.92% in group B), showed significant difference in each group post therapy (reduction to 20.83% in group A and to 31.25% in group B) but on comparing two groups, there was no significant difference seen (p=0.245). Out of total, 32.29% of patients presented with hirsutism for whom modified FG score was calculated, there was significant difference in improvement of hirsutism (p=0.001 in group A and p<0.0001 in group B) represented in Table 2, whereas no significant difference noticed on comparing two groups (p=0.982).

Table 1: Comparison of menstrual cycle between met and met+vit D_3 60k.

Menstrual cycle	Met (n=48)	Met+vit D_3 60k (n=48)	Total	P value
Pre therapy				
Normal	16 (33.33%)	13 (27.08%)	29 (30.21%)	0.505‡
Oligo	32 (66.67%)	35 (72.92%)	67 (69.79%)	
Post therapy				
Normal	38 (79.17%)	33 (68.75%)	71 (73.96%)	0.245‡
Oligo	10 (20.83%)	15 (31.25%)	25 (26.04%)	
P value	<0.0001‡	<0.0001‡	-	-

‡Chi square test

Table 2: Comparison of FG score between met and met+vit D_3 60k.

FG score	Met (n=13)	Met+vit D_3 60k (n=18)	Total	P value
Pre therapy				
Mean±SD	11±2.58	10.28±2.02	10.58±2.26	0.39*
Median (25-75th percentile)	10 (9-13)	10.5 (8-11)	10 (8-12)	
Range	8-15	8-15	8-15	
Post therapy				
Mean±SD	8.46±1.81	8.44±2.23	8.45±2.03	0.982*
Median (25-75th percentile)	8 (8-10)	9 (7-10)	9 (7-10)	
Range	6-12	5-13	5-13	
P value	0.001§	<0.0001§	-	-

*Independent t test, §Paired t test

Table 3: Comparison of acne between met and met+vit D_3 60k.

Acne	Met (n=48)	Met+ vit D_3 60k (n=48)	Total	P value
Pre therapy				
No	25 (52.08%)	24 (50%)	49 (51.04%)	0.838‡
Yes	23 (47.92%)	24 (50%)	47 (48.96%)	
Post therapy				
No	36 (75%)	35 (72.92%)	71 (73.96%)	0.816‡
Yes	12 (25%)	13 (27.08%)	25 (26.04%)	
P value	0.020‡	0.021‡	-	-

‡Chi square test

Table 4: Comparison of serum vitamin D between met and met+vit D_3 60k.

Serum Vitamin D	Met (n=48)	Met+vit D_3 60k (n=48)	Total	P value
Pre therapy				
Mean±SD	12.69±4.33	12.54±4.39	12.61±4.34	0.87*
Post therapy				
Mean±SD	14.85±6.21	28.65±6.5	21.75±9.38	<0.0001*
P value	0.018§	<0.0001§	-	-

*Independent t test, §Paired t test

Table 5: Comparison of total testosterone (ng/ml) between met and met+vit D_3 60k.

Total testosterone (ng/ml)	Met (n=48)	Met+vit D_3 60k (n=48)	Total	P value
Pre therapy				
Mean±SD	59.29±26.46	60.77±28.25	60.03±27.23	0.792*
Post therapy				
Mean±SD	55.02±24.3	55.56±24.36	55.29±24.2	0.913*
P value	0.0002§	0.0002§	-	-

*Independent t test, §Paired t test

Table 6: Comparison of glycemic parameters between met and met+vit D_3 60k.

Glycemic parameters	Met (n=48)	Met+vit D_3 60k (n=48)	Total	P value
Pre therapy fasting insulin (µIU/ml)				
Mean±SD	18.14±15.45	17.21±14.05	17.68±14.7	
Median (25-75th percentile)	16.32 (8.768-21.44)	13.14 (8.18-21.07)	16.08 (8.34-21.235)	0.758*
Range	3.12-99.71	4.12-67.29	3.12-99.71	
Post therapy fasting Insulin (µIU/ml)				
Mean±SD	16.61±12.78	16.49±12.66	16.55±12.66	
Median (25-75th percentile)	14.89 (8.805-19.368)	14.66 (8.83-18.195)	14.66 (8.83-18.902)	0.963*
Range	3.07-71.34	4.01-71.34	3.07-71.34	
P value	0.336§	0.577§	-	-
Pre therapy postprandial insulin (µIU/ml)				
Mean±SD	32.81±23.51	28.99±18.72	30.9±21.22	
Median (25-75th percentile)	27.82 (19.55-37.56)	25.37 (17.05-31.368)	26 (17.4-34.65)	0.381*
Range	4.06-99.38	4.06-81.53	4.06-99.38	
Post therapy postprandial insulin (µIU/ml)				
Mean±SD	30.58±22.6	27.01±16.31	28.79±19.68	
Median (25-75th percentile)	25.13 (17.8-35.692)	24.42 (17.2-30.925)	24.43 (17.2-34.19)	0.376*
Range	2.2-96.2	4.01-74.07	2.2-96.2	
P value	<.0001§	0.001§	-	-
Pre therapy HOMA-IR				
Mean±SD	4.62±4.68	4.39±3.69	4.51±4.19	
Median (25-75th percentile)	3.79 (2.238-5.522)	3.11 (1.72-5.748)	3.7 (1.802-5.632)	0.786*
Range	0.45-31.51	0.72-16.64	0.45-31.51	
Post therapy HOMA-IR				
Mean±SD	3.56±2.35	3.52±2.28	3.54 ± 2.3	
Median (25-75th percentile)	3.29 (2.135-4.595)	3.25 (1.742-4.395)	3.29(1.845-4.558)	0.926*
Range	0.68-13.09	0.83-10.34	0.68-13.09	
P value	0.017§	0.001§	-	-

*Independent t test, §Paired t test

Table 7: Comparison of ovary volume(cc) between met and met+vit D_3 60k.

Ovary volume (cc)	Met (n=48)	Met+vit D_3 60k (n=48)	Total	P value
Pre therapy right ovary volume (cc)				
Mean±SD	14.07±4.71	13.97±5.02	14.02±4.84	0.918*
Post therapy right ovary volume (cc)				
Mean±SD	11.71±3.51	11.77±3.88	11.74±3.68	0.934*
P value	<0.0001§	<.0001§	-	-
Pre therapy left ovary volume (cc)				
Mean±SD	14.56±5.01	14.42±5.16	14.49±5.06	0.889*
Post therapy left ovary volume (cc)				
Mean±SD	12.19±3.87	12.01±4.55	12.1±4.2	0.838*
P value	<0.0001§	<0.0001§	-	-

*Independent t test, §Paired t test

Table 8: Comparison of AFC between met and met+ vit D_3 60k.

AFC	Met (n=48)	Met+ vit D_3 60k(n=48)	Total	P value
Pre therapy				
Mean±SD	11.54±2.06	11.6±2.93	11.57±2.52	0.904*
Post therapy				
Mean±SD	10.31±1.57	10.02±2.25	10.17±1.93	0.463*
P value	0.0001§	<.0001§	-	-

*Independent t test, §Paired t test

Post therapy, in the group A and group B, there was significant difference noted in acne improvement from 47.92% to 25% and 50% to 27.08% respectively as represented in Table 3. In present study 42.71% of participants were overweight, out of which 43.75% were in group B and 6.25% of participants in group B were overweight. After giving metformin in group A, significant difference in improvement of BMI noted from mean of 24.13±3.11 to 23.2±2.65, similarly significant difference was noted in group B also, where mean value reduced from 24.63±4.06 to 23.53±3.56. However, on comparing outcomes in BMI of both groups, no significant difference was observed (p=0.6).

Table 4 shows that there was no significant difference in mean values of serum vitamin D in both groups pre therapy (12.69±4.33 in group A and 12.54±4.39 in group B), which after therapy improved to 28.65±6.5 in group B with significant difference (p<0.0001). Even, on comparing two groups significant difference was noted post therapy (p<0.0001).

Post therapy, in both group A and group B, there was significant difference in LH reduction (p<0.0001, p=0.0001), LH/FSH reduction (p<0.0001, p=0.0003), serum testosterone reduction shown in Table 5 (p=0.0002, p=0.0002).

However, on comparing the efficacy amongst the two groups, there was no significant difference.

Also there was significant difference in reduction of post prandial insulin after therapy. As shown in Table 6, significant difference was seen in improvement of HOMA-IR in both the groups (p=0.017 in group A and p=0.001 in group B).

Mean ovarian volume (>10 cc) reduced with significant difference in both groups with p<0.0001 in both groups as shown in Table 7. Whereas on comparison of two groups significant difference is not noted (p=0.934 and 0.838 in right and left ovarian volume respectively).

Similarly, Table 8 shows that AFC reduced with significant difference in both groups where mean AFC post therapy reduced from 11.6±2.93 to 10.02±2.25 in group B, but had no significant difference on comparing the two groups post therapy (p=0.463).

Most common side effect seen in group A was nausea and vomiting, whereas in group B was dizziness.

DISCUSSION

PCOS is a complex condition characterized by elevated androgen levels, menstrual irregularities, and/or small cysts in one or both ovaries. Prevalence of PCOS currently in Indian population ranges from 3.7 to 22.5% depending on population studied and the criteria used for diagnosis.[20,21] PCOS women have higher risks of endometrial cancer, cardiovascular disease, dyslipidemia and type 2 diabetes mellitus.[3,4] This draws attention to the need of early diagnosis and management of PCOS in adolescent girls.

Prevalence of vitamin D deficiency, is high as estimated in different studies worldwide.[5-8] Whereas, in India, community-based studies done previously have reported a prevalence ranging from 50% to 94%, which is very high.[9-16] Furthermore, in women with PCOS, vitamin D deficiency was observed in 70.3% women, 20.3% were vitamin D insufficient and only 9.4% were vitamin D sufficient in one study.[17]

Vitamin D is a steroid with hormone like activity that regulates function of over 300 genes and hence its supplementation has been extensively studied in various disease management worldwide.[18]

Thus, present study was carried out to see its effect after supplementation for 6 months in PCOS vitamin D deficient females. This was done by comparing their clinical, hormonal, metabolic and sonographic parameters before and after therapy.

Oligomenorrhea which was seen in approximately 66% of patients in group A and 72% in group B before therapy was reduced significantly to approximately 20% in group A and 31% in group B. So, there was an improvement in around 46% in group A and 42 % in group B. Similarly, such improvement was also seen in a study by Kadoura et al.[22] Hirsutism is another important clinical feature of PCOS, which was seen approximately in 13% and 18% in group A and B respectively before therapy which after supplementation improved significantly in both the groups. Similar results were seen in study by Al Bayyari et al who also concluded significant improvement in ovarian

volume and follicle number which was similar to the results shown in present study.[23] Acne before therapy was seen in nearly 48% and 50% in group A and group B respectively which reduced to 25% and 27% in group A and group B respectively after therapy in present study. Acne inflammatory lesions were decreased by 34.6 % after 8 weeks of vitamin D supplementation in a study done by Lim et al, which showed a greater improvement than the present study.[24] On comparing anthropometric parameters of the two groups post therapy in present study, mean weight in group A and B were significantly reduced. In the present study, mean BMI pre therapy in group A was 24.13±3.11 and 24.63±4.06 in group B which reduced significantly after therapy 23.2±2.65 and 23.53±3.56 in group A and B respectively ($p<0.0001$, $p<0.0001$). Both groups had similar anthropometric results in present study. However, a study done by Raziah et al concluded reduction in BMI in group which was supplemented with calcium and vitamin D 100000 IU per month.[25] Effect of vitamin D supplementation on BP has been studied in present study and in study by Pal et al as well where they concluded that significant lowering in BP parameters was seen in overweight and vitamin D deficient PCOS females with baseline BP≥120/80 mmHg (n=8) and in those with baseline serum 25OHD ≤20 ng/ml (n=9).[26] This was similar to the results shown in present study, but on comparing the two groups there was no significant difference. However, no significant improvement was seen in diastolic BP in both groups. Before therapy 30% participants had vitamin D <10 ng/ml and 67% had serum vitamin D in range of 10-20 (vitamin D insufficiency). In current study after supplementing vitamin D, its deficiency corrected significantly ($p=0.0001$). Similar results were shown by studies done by Kadoura et al, Asemi et al, Abootorabi et al, Trummer et al.[22,27-29] In the current study we did a baseline and post therapy for LH, FSH, LH/FSH, total testosterone, glycemic parameters- fasting, post prandial blood sugar, fasting and post prandial insulin, HOMA-IR. LH/FSH ratio improved in 23% of participants. Total testosterone improved in 19.5% participants. Improvement after therapy in both groups for all the above parameters was significant. But on comparing the two groups there was no significant difference. Similarly, a study by Karadag et al showed negative correlations between 25(OH)D levels and total testosterone ($r=-0.306$; $p<0.01$).[30] Since the main mechanism of action of vitamin D in PCOS females lies in improving insulin resistance, therefore we focused on including major glycemic parameters into our study. INDIA having estimated 77 million of population affected with diabetes, is a second most affected nation in the world. The risk is increased much more in PCOS females. Among all glycemic parameters that were studied in present study, post prandial blood sugars were deranged (>140) in most participants (35.42%). In present study, a significant improvement was seen in fasting and postprandial blood sugar and also in postprandial insulin. Pretherapy HOMA-IR >2.5 was seen in around 69% participants in group A and 58% in group B. After therapy significant improvement occurred in HOMA-IR with $p=0.017$ in group A and $p=0.001$ in group B. Likewise, some studies had similar observations, like study done by Abootorabi et al, concluded significant decrease in fasting plasma glucose ($p=0.001$).[31] Metabolic syndrome in PCOS can be diagnosed after evaluating lipid profile, for which we investigated the levels of triglycerides, total cholesterol, LDL, HDL. In present study, total cholesterol >200 mg/dl was seen in 5.21%, increased triglycerides in 10.42%, improvement in lipid profile was seen significantly in supplementation group. Triglycerides improved similarly as study done by Wehr et al and Asemi et al.[32,33] Most common side effect experienced by participants in group A was nausea and vomiting (29.17%) whereas in group B, it was dizziness (22.92%).

The side effects were minor and no patient discontinued the therapy because of the side effects.

CONCLUSION

Baseline (pre therapy) and post therapy investigations were done and following conclusions were made: both the groups had a significant improvement in clinical profile (menstrual cycle pattern, acne, hirsutism) of PCOS patients; waist hip ratio (WHR), BMI also improved in both the groups equally and significantly; serum vitamin D levels normalized significantly in group B; both groups were equally effective in improving hormonal parameters like: LH/FSH ratio, serum total testosterone; although not statistically significant, but a better response was seen with group B in terms of improving polycystic morphology on sonography; effect of vitamin D supplementation on mitigating the metabolic parameters was significant; vitamin D has a role in reducing insulin resistance by acting on pancreatic beta cells, which was confirmed in the present study, as in group B, on supplementing vitamin D showed better reduction in fasting and post prandial sugar levels than group A, also a significant reduction in HOMA-IR was seen; group B showed better lipid profile after therapy than group A though not statistically significant; and group B had better safety profile than group A in terms of side effects.

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