International Journal of Current Research and Academic Review

ISSN: 2347-3215 Volume 3 Number 8 (August-2015) pp. 453-460

www.ijcrar.com

Evaluating effect of Calcium/Vitamin D supplements on cardio metabolic risk factors in infertile women with polycystic ovary

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KEYWORDS

Infertility,
PCO,
Treatment,
Metabolic Syndrome,
Calcium,
Vitamin D

A B S T R A C T

The aim of this study was to compare the effect of Calcium/Vitamin D supplements on cardio metabolic rick factors in infertile women with polycystic ovary syndrome. In a clinical trial performed at obstetrics and gynecology department of Hamadan University of Medical Sciences on women visiting infertility clinic of Fatemiyeh Hospital for treatment of infertility, we compared treatment effects of the Calcium/Vitamin D supplements on cardiometabolic factors in infertile women with PCOS. This 12 week randomized parallel group trial was conducted to compare the effect of Calcium/Vitamin D supplements on cardio metabolic rick factors in infertile women with polycystic ovary syndrome. In this study 72 patients were randomized to the Metformin & Calcium/Vitamin D (37) and Metformin (35) groups. The numbers discontinuing the study prematurely were not ststistically different between three groups.The mean changes of cardiometabolic factors(HDL,LDL and …) were comapred between three groups. Per protocol analysis was done for comparing treatment groups (37 and 35 patients in Metformin & Calcium/Vitamin D and Metformin groups), respectively. Many of the metabolic factors(BMI, BP,FBS,LDL,and cholestrol) have been decreased significantly in two groups after treatment($p<0.001$). In all patients, 5 patients had metabolic syndrome. Significant differences were not observed in the studied parameters between patients with and without metabolic syndrome.

Introduction

Poly cystic ovary syndrome (PCOS) is considered one of the most common endocrine disorders of women in reproductive age with an estimated prevalence rate of 10-15% (1).

PCOS is associated with multiple cardiovascular risk factors such as insulin resistance, central obesity, hypertension, impaired glucose tolerance, type 2 diabetes, metabolic syndrome, infertility, endometrial hyperplasia, endometrial and ovary cancers.(2-3) Moreover, it is associated with nontraditional markers of cardiovascular risk, including inflammation, thrombosis, oxidative stress, sleep apnea, endothelial dysfunction, and arterial stiffness.(4,5)

The role of calcium (500 mg) and Vitamin D (400 unit) consumption and its deficiencies in different features of PCOS have been studied in some previous studies.(6,7,8) Their effectiveness is mainly due to their effect on body weight and follicular maturation. Both calcium and Vitamin D deficiency are considered as potential risk factors for obesity (6,7,8).

Vitamine-D(Vit-D) plays a role in adjustment of insulin secretion and glucose metabolism, and its shortage is related to insulin resistance, glucose intolerance, hypertension, and metabolic-syndrome (9-13). Studies conducted in the area of investigation of effects of Vit-D on cardiovascular diseases are contradictory (14-15).

The aim of this study was to compare the effect of Calcium/Vitamin D supplements on cardio metabolic rick factors in infertile women with polycystic ovary syndrome.

Materials and methods

In a clinical trial performed at obstetrics and gynecology department of Hamadan University of Medical Sciences on women visiting infertility clinic of Fatemiyeh Hospital for treatment of infertility, we compared the effect of Calcium/Vitamin D supplements on cardio metabolic rick factors in infertile women with polycystic ovary syndrome.

The clinical trial was performed on 20-45 year-old women visiting infertility clinic of Fatemiyeh Hospital in Hamadan for treatment of infertility.

The criteria for diagnosis of PCOS were Rotterdam criteria.

Inclusion criteria included abnormal menstrual cycles (oligomenorrhea and amenorrhea), polycystic ovary in sonography, chemical or clinical symptoms of hyperandrogenism (hirsutism and acne). Exclusion criteria of the study included history of any underlying and chronic disease (chronic kidney disease, etc.), history of abdominal and pelvic surgery, abnormal hysterosalpingography, abnormal serum prolactin level, smoking, pregnancy, current or previous Statin use during the past 2 months, insulin use, use of corticosteroids, anti-obesity medication, and history of neoplastic diseases.

The selected individuals were divided in simple random form into 2 groups, and underwent treatment for 12 weeks. As Metformin is considered as part of the routine treatment in infertility, all patients in all groups also received 1500 milligrams of Metformin every day along with the supplements received.

First group: under treatment with 1000 milligrams of Calcium and Vit-D-400 IU twice a day.

Second group: who were under treatment only with Metformin (11).

The sampling method was the simple sampling method, and any individual with the inclusion criteria of the study was gradually included in the study. Random assignment was performed with the block-randomized method as follows. 5 pieces of paper reading Calcium & Vit-D and 5 pieces of paper reading Metformin were placed in a plastic bag and mixed, and then, for each patient included in the study, one piece of paper would be taken out of the bag, and the patient would be assigned one of the groups based on what was written on it, and the procedure would be followed for 15 patients, and then, the other patients were selected with this procedure.

Blood samples were taken from all groups at the beginning of the study after 8 to 12 hours of nighttime fasting. All of the cardiometabolic factors such as systolic blood pressure, diastolic blood pressure, blood sugar, insulin, total cholesterol, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), testosterone, and Dehydroepiandrosterone (DHEA) as well as the serum level of the received supplement were examined. At the end of the treatment period, blood samples were again obtained after nighttime fasting to measure the aforementioned cardiometabolic factors as well as the received supplement.

Adult Treatment Panel III (ATP-III) criteria:

1. A waist circumference of more than 102 cm in men and 88 cm in women
2. A triglyceride level over 150 or administration of drugs for the treatment of high TG
3. An HDL level below 40 or administration of drugs for the treatment of low HDL
4. An FBS level higher than 100
5. A Blood pressure (BP) higher than 130/80 or administration of Hypertension (HTN) drugs.

Patients who met three of the aforementioned five criteria were diagnosed with the metabolic syndrome. The waist circumference of patients was measured in centimeters by the project resident. In the Metformin & Calcium/Vitamin D group one patient was excluded from the study because of headache and recommendation of an internist. In the Metformin group, 2 patients were excluded for their unwillingness to consume drugs, 3 were omitted because of diarrhea and one was excluded because of pregnancy using Intracytoplasmic Sperm Injection (ICSI).

Ethical Considerations

All of the patients participated voluntarily in this study and the required information was presented to all of the patients under study in a comprehensible way. The patients were included in the study after completing the informed consent form which was approved by the ethics and research committee of the university. Patients were charged no additional costs and all of the medications and supplements were provided to the patients for free. All patients were free to leave the study and all of the information will remain confidential.

Statistical Analysis

The collected data were analyzed by SPSS-17 statistical software. The collected data were expressed as percentage and mean ± SD. Continuous (quantitative) variables were compared by Independent samples, Paired T test and ANOVA test. Categorical (qualitative) variables were compared by contingency tables and Chi-square test or Fisher's exact test. P-value ≤ 0.05 was considered statistically significant.

Possible Problems and Solutions

Lack of patient's consent: In order to solve this problem, we talked to the patients to the possible extent and provided them with the required explanations. Their questions about the study were also answered properly in order to win their consent and encourage them to participate in the study with full consent.

Result and Discussion

This clinical trial that was carried out in the Department of Obstetrics and Gynecology of Hamedan University of Medical Sciences on women who visited the infertility clinic

of Fatemiyeh Hospital to receive treatment for infertility. The effects of supplementary treatments (including Calcium/Vitamin D) on the cardiometabolic factors of infertile women with PCOS were examined and compared. The following results were obtained from the examinations:

In this study, 72 patients were studied. Of the 72 patients, 37 were put in the Metformin & Calcium/vitamin D group and 35 were put in the Metformin group. Finally, 6 patients were excluded from the study while 36 patients in the Metformin & Calcium/Vit D group and 30 in the Metformin group finished the study.

The mean age of patients in the Metformin & Calcium/Vit D group and the Metformin group was 26.75 ± 5 and 27 ± 4.49 years, respectively (P=0.829). Results of analysis of other demographic parameters of patients are presented in Table (1). According to the ATP-III criteria, the metabolic syndrome was observed in 5 patients. Of the patients with the metabolic syndrome, 2 were in the Metformin & Calcium/Vit D group and 3 in the Metformin group (P=0.107).

Table (2) shows the changes in the parameters under study after the treatment as compared to the parameters before the treatment. Results presented in this table suggest that no significant difference existed between the changes in the levels of the following parameters in the three groups: Body Mass Index (BMI) (p=0.854), SBP (p=0.876), DBP (p=0.416), FBS (p=0.153), cholesterol (p=0.143), TG (p=0.490) and DHEA-S (p=0.987). In addition, the increase in the level of HDL was significantly higher in the Metformin & Calcium/Vit D group (P<0.001). The increase in the level of blood testosterone was significantly higher in the Metformin group (P=0.037).

In this clinical trial, we evaluated the effect of Metformin and combination of Metformin with Vitamin D/Calcium on cardio metabolic rick factors in infertile women with polycystic ovary syndrome(PCOS).

Several studies investigated different therapeutic strategies of PCOS because PCOS is very common and can change the life style PCOS often with obesity and hirsutism and irregular menstruation that can very important for a person (16-17).

Many studies have demonstrated the potential improving effects of combined Vitamin D and calcium supplementation on PCOS symptoms such as infertility, regularity of menstrual cycles, BMI, insulin resistance and features of hyper androgenism.(4,5,18) Recently in a review study Galusha concluded that though their positive effects in this field have been reported in many studies, but there are many controversies in this regard and quality of evidences are not satisfactory enough.(2)

Hans, in the current study, we evaluated the effectiveness of Vitamin D and calcium as supplement therapy in addition to routine metformin therapy. In a similar study in Yazd-Iran, Firouzabadi *et al*. have compared the effectiveness of metformin and metformin plus Vitamin D and calcium supplementation on PCOS symptoms of 100 women. The treatment period was 6 months. They concluded that Vitamin D and calcium supplementation have a positive effect on BMI, follicular maturation, regularity of menses, androgen related symptoms, infertility and insulin resistance specially in women with Vitamin D deficiency. The limitation of their study was lack of a control group (4).

Table.1 Demographics finding of patients in two groups

	Groups		P
	Metformin & Calcium/Vitamin D	Metformin	
Age(year)	26.76 ± 5.00	27.00 ± 4.49	0.829
Height(cm)	161.70 ± 3.79	158.80 ± 5.18	0.008
Weight(kg)	69.96 ± 10.58	67.54 ± 12.81	0.385
Waist Circumference(cm)	82.59 ± 8.99	80.09 ± 11.18	0.296
Hip Circumference(cm)	103.59 ± 8.10	101.00 ± 11.91	0.281
Duration of infertility(month)	4.01 ± 2.80	5.01 ± 3.94	0.216

Table.2 Analysis of the studied parameters among the two groups

	Groups		P
	Metformin & Calcium/Vitamin D	Metformin	
BMI	-0.41 ± 0.50	-0.38 ± 0.56	0.854
SBP(mmHg)	-3.92 ± 9.66	-4.22 ± 5.25	0.876
DBP(mmHg)	-2.36 ± 6.81	-3.59 ± 5.42	0.416
FBS(mg/dl)	-3.50 ± 5.85	-5.27 ± 3.53	0.153
LDL(mg/dl)	-5.31 ± 6.94	-4.37 ± 4.08	0.516
Cholesterol(mg/dl)	-23.36 ± 26.79	-15.10 ± 15.92	0.143
HDL(mg/dl)	2.39 ± 3.13	-.98 ± 4.13	<0.001
TG(mg/dl)	-4.90 ± 30.16	-8.70 ± 11.60	0.490
Testosterone	-0.08 ± 0.21	0.03 ± 0.19	0.037
DEAH-S	0.02 ± 0.25	0.02 ± 0.14	0.987

Some studies support the effect of vitamin D deficiency on pathophysiology of PCOS and even insulin resistance (19-21). Pal *et al* found that 3 months supplementation with vitamin D and calcium (Ca) can reduce androgens. They believe that vitamin D and Ca have a direct effect on the ovarian and/or adrenal steroid genesis pathway (22). Firouzabadi *et al* also found calcium and vitamin D supplementation can make a positive effect on weight loss, follicle maturation, menstrual regularity, and improvement of hyperandrogenism, in infertile women with PCOS (23). According to Thys-Jacobs *et al* calcium hemostasis disturbance can cause follicle growth disorders (24).

In several studies, the relationship between diet and its components and risk of different diseases has been proven. Studies suggest that use of food with high glycemic indexes such as white bread, rice, and drinks with cola is accompanied by increase in risk of type 2 diabetes in women (28-29). The role of Vit-D and Calcium in insulin secretion and insulin resistance has been demonstrated in different studies and in human and animal models (25-27).

With multiple studies on animals, the role of Calcium in oocyte maturation has also become apparent, but it is unknown how this effectiveness works, and researchers find necessity of effectiveness of Calcium and Vit-D on human ovulation (particularly in

cases of PCOS) an important item to be examined and studied (28-30).

In this study, we also examined the effects of simultaneous reception of Calcium, Vit-D, and Magnesium as supplement on patients with PCOS, and the results suggest the effectiveness of use of these supplements in suffering patients. In a study performed by Yacob on patients with PCOS, Vit-D shortage was observed in the individuals, and in these patients, despite normal extracellular Calcium concentration, decrease in intracellular Calcium serum concentration and also abnormal operation of the oocyte were observed following Vit-D decrease (30). And this study emphasizes that extracellular Calcium concentration cannot suggest normal intracellular Calcium (30).

In the present study, particularly in regard to HDL, the post-treatment increase rate was significantly higher in the Metformin & Calcium/Vit-D group patients than in the Metformin group patients, and with the other parameters, although the Metformin & Calcium/Vit-D group had better conditions than the Metformin group in some cases, there was no significant difference between the patients in the two groups.

In the present study, 5 patients among all suffered metabolic-syndrome before the study, which means lower incidence of metabolic-syndrome in our study than in the above studies, and there was also no significant difference between rates of changes in the parameters under study in the patients with and without metabolic-syndrome. In our study, the HDL increase and testosterone decrease rates were significantly higher in the patients receiving Calcium.

Conclusion

In this study 72 patients were randomized to the Metformin & Calcium (37) and Metformin (35) groups. The numbers discontinuing the study prematurely were not statistically different between three groups. The mean changes of cardiometabolic factors (HDL,LDL and …) were compared between three groups.
Per protocol analysis was done for comparing treatment groups (37 and 35 patients in Metformin & Calcium and Metformin groups), respectively. Many of the metabolic factors (BMI, BP, FBS, LDL and cholestrol) have been decreased significantly in two groups after treatment($p<0.001$).

In all patients, 5 patients had metabolic syndrome. Significant differences were not observed in the studied parameters between patients with and without metabolic syndrome.

References

1.Gibbs R, Karian B, Haney A, Nygaard I. Philadelphia: Lippincott Williams and Wilkins; 2008. Danforth's Obstetrics and Gynecology; p. 655. 661.

2.Fritz M, Speroff L. Philadelphia: Lippincott Williams and Wilkins; 2011. Clinical Gynecologic Endocrinology and Infertility; pp. 512–8. 523, 525, 29, 728-34.

3.Cohen D. Amenorrhea. In: Berek J, editor. Berek and Novak's Gynecology. Vol. 2. Philadelphia: Lippincott Williams and Wilkins; 2012. pp. 1050–6.

4.Firouzabadi RD, Aflatoonian A, Modarresi S, Sekhavat L, Mohammad Taheri S. Therapeutic effects of calcium & vitamin D supplementation

in women with PCOS. Complement Ther Clin Pract. 2012;18:85–8.

5.Rashidi B, Haghollahi F, Shariat M, Zayerii F. The effects of calcium-vitamin D and metformin on polycystic ovary syndrome: A pilot study. Taiwan J Obstet Gynecol. 2009;48:142–7.

6.Hahn S, Haselhorst U, Tan S, Quadbeck B, Schmidt M, Roesler S, et al. Low serum 25-hydroxyvitamin D concentrations are associated with insulin resistance and obesity in women with polycystic ovary syndrome. Exp Clin Endocrinol Diabetes. 2006;114:577–83.

7.Muscogiuri G, Sorice GP, Prioletta A, Policola C, Della Casa S, Pontecorvi A, et al. 25-Hydroxyvitamin D concentration correlates with insulin-sensitivity and BMI in obesity. Obesity (Silver Spring)2010;18:1906–10.

8.Wehr E, Pilz S, Schweighofer N, Giuliani A, Kopera D, Pieber TR, et al. Association of hypovitaminosis D with metabolic disturbances in polycystic ovary syndrome. Eur J Endocrinol. 2009;161:575–82.

9.Kotsa k, Yavropoulou M.P, Anastasiou O, Yovos J.G. Role of vitamin D treatment in glucose metabolism in polycystic ovary syndrome. Fertility and Sterility 2009; 92(3): 1053-8.

10.Wehr E, pieber TR, Obermayer- Pietsch B. Effect of vitamin D3 treatment on glucose metabolism and menstrual frequency in PCOS women-a pilot study. J Endocrinol Invest 2011;24 : 153-159.

11.Selimoglu H, Duran C, kiyici S, Ersoy C, Guclu M, Ozkaya G, Tuncel E, Erturk E, Imamoglu S, The effect of vitamin D replacement Therapy on insulin resistance and androgen levels in women with polycystic ovary syndrome. J Endocrinol Invest 2010; 33(4): 234-8.

12.Li HWR, Brereton R.E, Anderson R.A, Wallace A.M, Ho C,K.M. vitamin D deficiency is common and associated with metabolic risk factors in patients with polycystic ovary syndrome Metabolism 2011; 03.002.

13.Parker J, Hashmi O, Dutton D, Mavrodaris A, stranges S, Kandala NB, Clarke A, france OH. Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis. Maturitas. 2010; 65(3): 225-36.

14.Pittas AG, chung M, Trikaltions T, Mitra J, Brendel M, Patel K, Lichtenstein AH, Lau J, Bal EM. Systematic review :vitamin D and cardiometabolic outcomes. Ann Intern Me 2010; 152 (5): 307-14.

15.Champagne CM. Magnesium in hypertention, cardiovascular disease, metabolic syndrome and other conditions: a review. Nutr Clin pract 2008; 23 (2): 142-51.

16. Setji TL, Brown AJ. Polycystic ovary syndrome: Update on diagnosis and treatment. Am J Med. 2014

17. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol. 2013;6:1–13.

18. Galusha AM. Improvement of Symptoms in Patients with Polycystic Ovarian Syndrome by vitamin D and Calcium Supplementation. School of Physician Assistant Studies. Paper. 2013;461

19.Mahmoudi T, Gourabi H, Ashrafi M, Yazdi RS, Ezabadi Z. Calciotropic hormones, insulin resistance, and the polycystic ovary syndrome. Fertil Steril. 2010;93:1208–1214.

20.Selimoglu H, Duran C, Kiyici S, Ersoy C, Guclu M, Ozkaya G, et al. The effect of vitamin D replacement therapy on insulin resistance and

androgen levels in women with polycystic ovary syndrome. J Endocrinol Invest. 2010;33:234–238.

21.Liu E, Meigs JB, Pittas AG, Economos CD, McKeown NM, Booth SL, et al. Predicted 25-hydroxyvitamin D score and incident type 2 diabetes in the Framingham Offspring Study. Am J Clin Nutr.2010;91:1627–1633.

22.Pal L, Berry A, Coraluzzi L, Kustan E, Danton C, Shaw J, et al. Therapeutic implications of vitamin D and Calcium in overweight women with Polycystic Ovary Syndrome. Gynecol Endocrinol. 2012;28:965–968.

23.Firouzabadi Rd, Aflatoonian A, Modarresi S, Sekhavat L, MohammadTaheri S. Therapeutic effects of calcium & vitamin D supplementation in women with PCOS. Comp Ther Clin Pract. 2012;18:85–88.

24.Thys-Jacobs S, Donovan D, Papadopoulos A, Sarrel P, Bilezikian JP. Vitamin D and calcium dysregulation in the polycystic ovarian syndrome. Steroids. 1999;64:430–435.

25.Billaudel BJ, Bourlon PM, Sutter BC, Faure-Dussert AG. Regulatory effect of 1,25-dihydroxyvitamin D3 on insulin release and calcium handling via the phospholipid pathway in islets from vitamin D–deficient rats. J Endocrinol Invest 1995; 18(9):673–682.

26.Jorde R, Sundsfyord J, Haug E, Bonaa KH. Relation between low calcium intake, parathyroid hormone, and blood pressure. Hypertention 2000;35: 1154-9.

27.Bostick RM, Kushi LH, Wu Y, Meyer KA, Sellers TA, Folsom AR. Relation of calcium, vitamin D, and dairy food intake to ischemic heart disease mortality among postmenopausal women. Am J Epidemiol 1999; 149:151-61.

28.Gluek C, Pappana R, Wang P, Goldenberg N, Sieve- Smith L. Incidence and treatment of metabolic syndrome in newly referred women with confirmed polycystic ovarian syndrome. J Clin Endo Metab 2003; 52:908-15.

29.Azizi F, Salehi P, Etemadi A, Zahedi-asl S. Prevalence of metabolic syndrome in an urban population: Tehran lipid and glucose study, Diabetes Res Clin Pract 2003; 61:29-37.

30.Ardabili HR, Gargari BP, Farzadi L. Vitamin D supplementation has no effect on insulin resistance assessment in women with polycystic ovary syndrome and vitamin D deficiency . Nutrition Research. 2012;32: 195-201