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**INTERNATIONAL JOURNAL OF
 ADVANCED RESEARCH (IJAR)**

Article DOI: 10.21474/IJAR01/3938
 DOI URL: <http://dx.doi.org/10.21474/IJAR01/3938>



RESEARCH ARTICLE

SIGNIFICANCE OF VITAMIN –D AND INSULIN RESISTANC IN POLYCYSTIC OVARIAN SYNDROME IN MANIFESTING RHEUMATOID ARTHRITIS.

T.Uma^{1*}, D.S.S.Girija Vani² and R. Vijayaraghavan³.

1. Department Of Biochemistry Ph.D scholar Saveetha University, Chennai, Tamilnadu, India.
2. Department Of Biochemistry , Saveetha University, Chennai, Tamilnadu, India..
3. Director Of Research, Saveetha University, Chennai, Tamilnadu, India.

Manuscript Info

Manuscript History

Received: 12 February 2017
 Final Accepted: 15 March 2017
 Published: April 2017

Key words:-

Insulin resistance, Oxidative stress, PCOS

Abstract

Aim& objectives: Polycystic ovary syndrome (PCOS) is the most common female endocrine disorder; It is a heterogeneous androgen excess disorder with different degrees of reproductive and metabolic dysfunctions. The objective of this study is to determine whether serum vitamin D and insulin resistance manifest to Rheumatoid Arthritis in women with PCOS are not.

Materials and methods:- The study includes total of 80 Subjects within the age group of 20 to 50years were selected and divided into two groups. Group I consisted of 50 diagnosed female patients of PCOD. 5 ml of blood sample was obtained from the participant under all aseptic precautions after 12 hours of fasting . 2ml is transferred to EDTA and remaining blood in plain tubes allowed to clot at 1 hour and centrifuged at 2000rpm for 10mins to obtain serum. The Serum samples are collected for estimation of glucose, Insulin, vitamin D, insulin resistance index (HOMA - IR), and anti-CCP are analysed

Results: Women with PCOS had significantly higher FBS(112±15.9) (P<0.01) than the control subjects(83.30±11.95), Women with PCOS had significantly higher insulin values (23±.9) (P<0.01) than the control subjects(83.30±11.95), Women with PCOS had significantly higher HOMA-IR(112±15.9) (P<0.01) than the control subjects(83.30±11.95), Women with PCOS had significantly higher VITAMIN -D(112±15.9) (P<0.01) than the control subjects(83.30±11.95).

Conclusion: Vitamin D is not only a regulator of bone and mineral metabolism, but also a potent immunomodulator linked to many major human diseases including glucose homeostasis and insulin resistance. Insulin resistance encourages oxidative stress because hyperglycemia and higher levels of free fatty acids lead to ROS production. Thus, insulin may defend against pro-inflammatory responses to hyperglycemia by acting as an anti-inflammatory agent. Proinflammatory cytokines seem to have beneficial effects on the insulin resistance observed in patients with RA and hormonal mechanisms involved in RA.

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Corresponding Author:- T.Uma.

Address:- Department Of Biochemistry Ph.D scholar Saveetha University, Chennai, Tamilnadu, India.

Introduction:-

Polycystic ovary syndrome (PCOS) is the most common female endocrine disorder; It is a heterogeneous androgen excess disorder with different degrees of reproductive and metabolic dysfunctions. Metabolic disturbances including insulin resistance, hyperinsulinemia and dyslipidemia, are common features in the majority of women with PCOS. Women with PCOS may also be at elevated risk of vitamin D deficiency (VDD). In contrast to a prevalence of 20%–48% among the general adult population, a relative higher prevalence of VDD is observed among women with PCOS. Additionally, positive associations of VDD with some well-known comorbidities of PCOS including type 2 diabetes, insulin resistance, metabolic syndrome, and cardiovascular diseases, are reported. In this regard, an increasing number of studies have been conducted to investigate the specific relationship between vitamin D status and PCOS. (1)

Vitamin D may play a role in glucose metabolism by enhancing insulin synthesis and release, and increasing insulin receptor expression or suppression of proinflammatory cytokines that possibly contribute to the development of insulin resistance [2]. The effect of vitamin D on metabolic and reproductive dysfunctions in PCOS may be mediated by insulin resistance. Reproductively, insulin resistance increases hyperandrogenism through insulin increasing ovarian androgen production, and reducing sex hormone-binding globulin (SHBG) production [3]. Metabolically, insulin resistance is associated with an increased risk for impaired glucose tolerance, type 2 diabetes mellitus and cardiovascular disease [4]. Therefore, vitamin D may play a key role in the development of PCOS.

Insulin resistance is a common feature of PCOS affecting 50-70% of women with the disorder. Polycystic ovary syndrome (PCOS) is an exceptionally common disorder of premenopausal women characterized by hyperandrogenism and chronic anovulation. Its etiology remains unknown. A biologic response to insulin that is less than normal is defined as insulin resistance. A relationship between insulin and hyperandrogenism has been observed from several different vantage points. hyperinsulinemia play important roles in the pathogenesis of PCOS (Dunaif A, 1997). (5) IR and hyperinsulinemia appears to interfere with ovarian steroidogenesis defects as well as anovulatory mechanism (Poretsky L P-999). These two factors produce the hyperandrogenism interfering with pituitary ovarian axis, leading to increased LH levels, anovulation, amenorrhea and infertility. PCOS is associated with an increased risk of metabolic complications including impaired glucose tolerance, type 2 diabetes, hypertension, dyslipidemia. Several studies have documented that at least 30-40% of PCOS patients were obese or over weight and obesity has an aggravating role in PCOS. (Diamantri – Kandarakis et al 1999, Azziz et al 2004)

Materials and Methods:-

The study was approved by the institutional Human Ethical Committee (IHEC) at saveetha university. Informed consent was obtained from participants. The objectives of the study were explained and a written concept was taken from each subject. The data on family history and personal history were collected through standard questionnaire.

Permission was also taken from hospital for sample & data collection and analysis. 5 ml of blood sample was obtained from the participant under all aseptic precautions. The study was carried out at Rajiv Gandhi Institute Of Medical Sciences & general hospital, Srikakulam, Andhra Pradesh in collaboration with Department of Obstetrics and Gynecology. The study includes the patients diagnosed as PCOD by using revised diagnostic criteria (Rotterdam criteria) two of the three criteria is required to be present Oligomenorrhea/amenorrhea, Polycystic ovaries on ultrasound, Clinical or biochemical signs of hyperandrogenism. Diagnosed cases of diabetes mellitus, thyroid dysfunction, Cushing's syndrome, congenital adrenal hyperplasia, hyperprolactinemia, androgen secreting tumor. Subjects taking medicines like ovulation induction agents, hormonal drugs and current or previous use of oral contraceptives within last 6 months are excluded from the study. Based on inclusion and exclusion criteria, a total of 80 Subjects within the age group of 20 to 50 years were selected and divided into two groups. Group I consisted of 50 diagnosed female patients of PCOD. Group II comprised of 30 control group with normal menstrual cycles.).

5 ml of blood sample was obtained from the participant under all aseptic precautions after 12 hours of fasting. 2ml is transferred to EDTA and remaining blood in plain tubes allowed to clot at 1 hour and centrifuged at 2000rpm for 10 minutes to obtain serum. The Serum samples for estimation of glucose by Glucose oxidase and peroxidase method which is analysed calorimetrically. Insulin, vitamin D and anti-ccc are analysis is carried out by chemiluminescence immunoassay by using Access 2, Beckman Coulter Manufactured by: Beckman Coulter, Inc. 4300 N. Harbor Blvd. Fullerton, CA 92835 U.S.A.

Insulin resistance will be measured by homeostasis model assessment insulin resistance index (HOMA - IR).
 HOMA-IR = Fasting serum insulin (mU/ml) x fasting plasma glucose (mmol/l)

22.5

Statistical Analysis:-

Data was expressed as mean ± S.D. For comparison of all quantitative variables between control and PCOS groups, the unpaired t-test was used and association between the parameters were assayed by Pearson correlation analysis. Statistical significance was accepted at P<0.05. All statistical analysis were performed using SPSS Program .

Sl.no	Variable	controls			PCOS			p-value SIGNIFICANCE
		N	Mean	S.D	N	Mean	S.D	
1	FBS	30	83.30	11.95	50	112.30	15.89	<0.01 HS
2	Insulin	30	15.50	2.87	50	23.38	5.39	<0.01 HS
3	HOMA-IR	30	3.20	0.82	50	6.62	2.15	<0.01 HS
4	Vitamin-D	30	59.63	12.41	50	31.32	5.24	<0.01 HS

Results:-

Women with PCOS had significantly higher FBS(112±15.9) (P<0.01) than the control subjects(83.30±11.95), Women with PCOS had significantly higher insulin values (23±.9) (P<0.01) than the control subjects(15.50±2.87), Women with PCOS had significantly higher HOMA-IR(6.62±2.15) (P<0.01) than the control subjects(3.20±0.82), Women with PCOS had significantly higher VITAMIN -D(31.32±5.24) (P<0.01) than the control subjects(59.63±12.41),

Group	Anti CCP		Total
	<17	>17	
Control	30	0	30
	100%	0%	100%
PCOD	44	6	50
	88%	12%	100%

Fisher exact test; p=0.05; S

Fig 1:- Comparison of patients with Controls - FBS-Glucose (Mean)

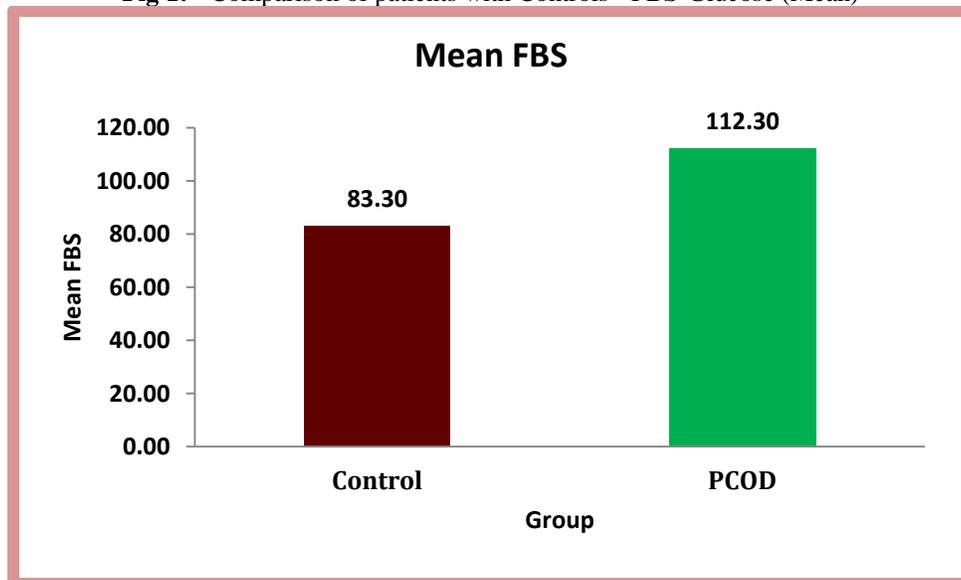


Fig 2:- Comparison of patients with Controls - Insulin (Mean)

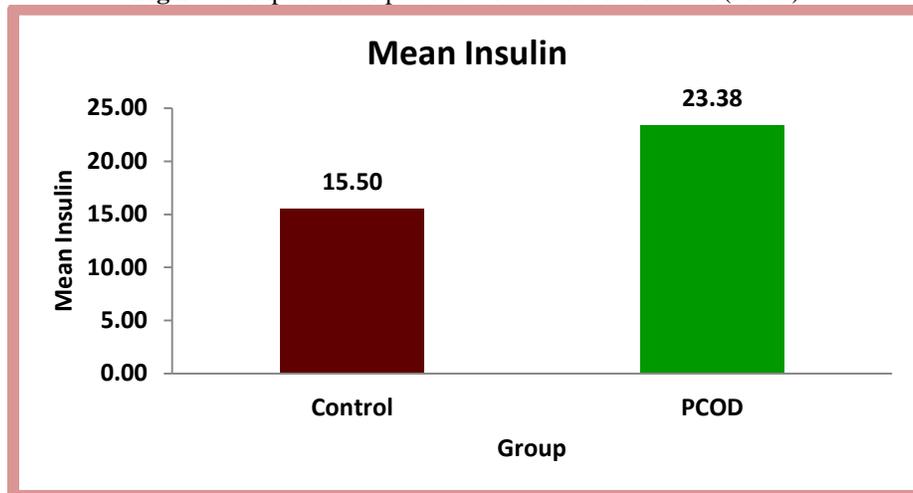


Fig 3:- Comparison of patients with Controls - HOMA IR (Mean)

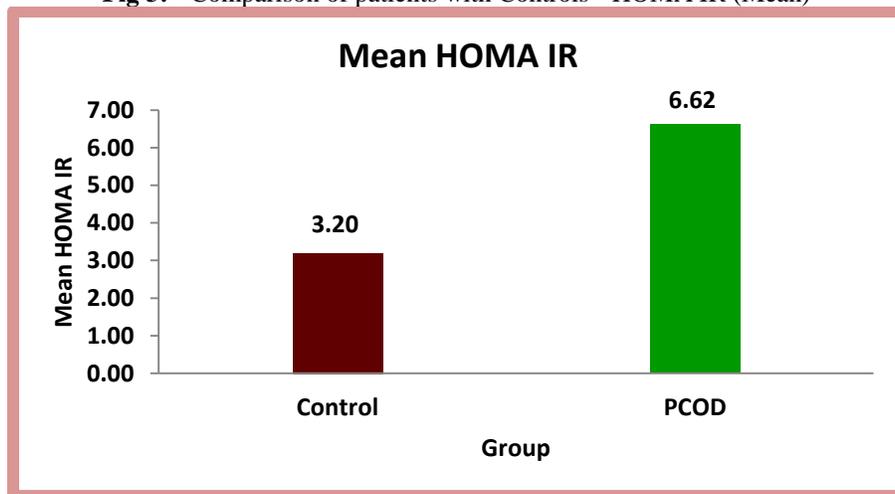


Fig 4:- Comparison of patients with Controls – vitamin-D (Mean)

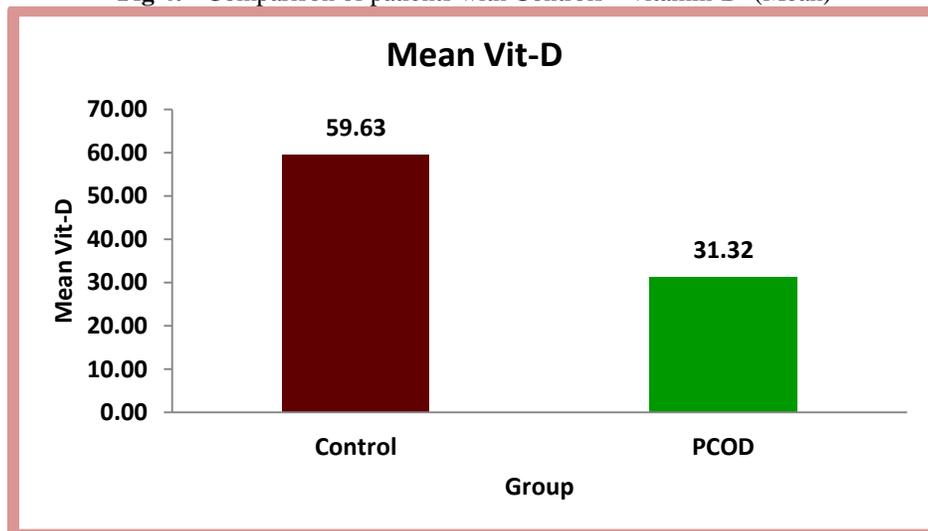
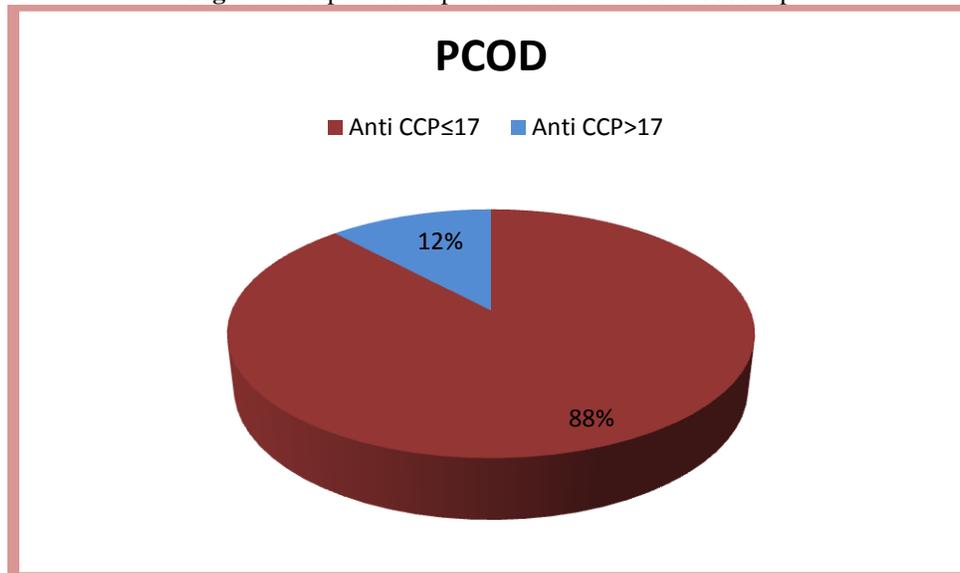


Fig 5:- Comparison of patients with Controls – Anti ccp



Discussion:-

The present study supports that serum vitamin D status is decreased in pcos which is related to metabolic and hormonal dysfunctions in women with PCOS. Low 25(OH)D levels are found to be significantly correlated with insulin resistance in women with PCOS. Among women with PCOS, those with vitamin D deficiency were more likely to have measures of dysglycemia compared to those without vitamin D deficiency. Similarly, lower vitamin D levels were positively correlated with markers of dysglycemia, support a significant difference in serum vitamin D levels between women with and without PCOS.(1)

Vitamin D deficiency (VDD) is common in women with and polycystic ovary syndrome (PCOS) and may be associated with metabolic and endocrine disorders in PCOS. There is much evidence, that in addition to sex steroid hormones, the classic regulators of reproduction, Vitamin also modulates Reproductive processes in women; its nuclear receptor has been identified in the uterus, oviduct, ovary, placenta, and fetal membranes. A recent observational study by Velija-Asimi *et al.* found that 68% (41 out of 60) PCOS patients had VDD, of which 54% ($n = 22$) were obese and 46% were non-obese ($n = 19$) [6]. Another study also reported a higher prevalence of VDD in obese women with PCOS than in lean women with PCOS (70% vs. 60%) [7].

There is some evidence suggesting that vitamin D deficiency may be involved in the pathogenesis of insulin resistance and metabolic syndrome in PCOS. The effects of vitamin D are mediated via both genetic and cellular pathways. Vitamin D regulates gene transcription through nuclear vitamin D receptors (VDR) that are distributed across various tissues, including skeleton, parathyroid glands and the ovaries. The pathogenesis of PCOS has been linked to the effects of VDRs (TaqI, BsmI, FokI, ApaI and Cdx2 polymorphisms) on LH and SHBG levels, testosterone levels, insulin resistance and serum insulin levels. Vitamin D deficiency increases PTH production, which is regulated through levels of serum calcium and vitamin D. It has been suggested that the combination of vitamin D deficiency and dietary calcium insufficiency may be largely responsible for the menstrual abnormalities associated with PCOS. The low calcium intake might also contribute to the hormonal dysregulation that occurs in PCOS. VDRs play an important role in oestrogen production in the ovary. Vitamin D regulates oestrogen biosynthesis through direct regulation of the expression of the aromatase gene and by maintaining extracellular calcium homeostasis. In human ovarian tissue, 1,25-dihydroxyvitamin D₃ stimulation of oestrogen and progesterone production and lack of effect on testosterone production may be explained by the augmentation of aromatase activity by vitamin D. Aromatase gene expression was decreased in PCOS follicles compared to controls, and they had increased levels of LH but decreased follicular production of progesterone and estradiol by preovulatory follicles, possibly because of the hyperluteinized microenvironment of PCOS follicles. As a result of these effects, vitamin D deficiency may exacerbate symptoms of PCOS.(8)

While the exact mechanism underlying vitamin D and insulin resistance is not known, multiple cellular and molecular mechanisms have been proposed to explain the relationship. The biologically active form of vitamin D, 1,25-dihydroxyvitamin D (1,25OHD) may enhance insulin action by enhancing insulin synthesis and release, increasing insulin receptor expression or suppression of proinflammatory cytokines that are believed to mediate insulin resistance. Vitamin D may also mediate insulin sensitivity by improving calcium status, increasing local production of 25OHD, which leads to transcriptional regulation of specific genes or suppressing serum levels of PTH. A recent study there is substantial evidence supporting a relationship between vitamin D status and insulin sensitivity.

Vitamin D levels have also been negatively associated with insulin resistance (fasting insulin and HOMA-IR). A study by Hahn *et al.*^[9] also found that when grouping the women with PCOS according to 25OHD levels, lower levels of 25OHD were associated with insulin resistance and obesity. It has been suggested that obesity may have a confounding role in the relationship between 25OHD and insulin resistance in women with PCOS. However, one study showed that women with PCOS with severe vitamin D deficiency were more insulin resistant, independently of BMI and WHR and another showed that while 25OHD levels were lower in obese women with PCOS, in both the obese and non-obese women, 25OHD levels were negatively correlated with BMI and HOMA-IR, Wehr *et al.* also investigated this relationship using a multivariate regression analysis and found 25OHD levels were a significant and independent predictor for HOMA-IR along with BMI. This study suggests lower 25OHD levels are associated with higher insulin resistance. (8)

Insulin resistance is an essential feature of MS that has been linked to RA [38]. In a study that included 94 patients with RA, Dessein and Joffe [9] observed that insulin resistance was associated with markers for inflammation such as C-reactive protein and erythrocyte sedimentation rate and disease activity scores. On the other hand, beta-cell function showed an inverse correlation with DAS28 and swollen and painful joint. Chung *et al.* [10] studied insulin resistance in 104 patients with RA and compared the results with those of 124 cases of systemic lupus erythematosus. They found that patients with RA have a higher insulin resistance index than systemic lupus erythematosus patients, and that insulin resistance was directly correlated with levels of interleukin 6, tumor necrosis factor-(TNF- α), C-reactive protein, and erythrocyte sedimentation rate or coronary calcification. Other studies have also confirmed the association between insulin resistance and RA.

Vitamin D has immunologic activity independent of its crucial role in calcium regulation. Animal models of autoimmune disease have shown beneficial effects of vitamin D as an immunosuppressant. For example, murine models of human RA demonstrated both decreased incidence and severity of disease in mice treated with active vitamin D. Evidence supporting an effect of vitamin D in RA specifically also is derived from clinical observations. Manolagas *et al.* found that a significantly greater proportion of seropositive RA patients (76%) had lymphocytes possessing vitamin D receptors compared with controls (18%). Within the rheumatoid joint, the active form of vitamin D has been shown to be synthesized in RA synovium and is thought to be stimulated by interleukin-1 (IL-1) and/or IL-2. Locally produced vitamin D may act in a paracrine manner to decrease T cell responsiveness through the inhibition of cellular proliferation and reduction in lymphokine production when confronted by an inappropriate and overly exuberant immune response.

Conclusion:-

Vitamin D is not only a regulator of bone and mineral metabolism, but also a potent immunomodulator linked to many major human diseases including glucose homeostasis and insulin resistance. The evidence suggests the role of vitamin D in the pathogenesis of insulin resistance including several vitamin-D-related gene polymorphisms and vitamin-D-related metabolic and immune pathways. Supplementations of vitamin D may provide for suitable management of insulin resistance. Insulin resistance encourages oxidative stress because hyperglycemia and higher levels of free fatty acids lead to ROS production. An increase in ROS generation resulting from hyperglycemia has been observed in women with PCOS [36], and insulin infusion in obese individuals has been shown to inhibit ROS production [37]. Thus, insulin may defend against pro-inflammatory responses to hyperglycemia by acting as an anti-inflammatory agent.

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