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Role of Vitamin-D and Oxidative Stress in Polycystic Ovarian Syndrome with Rheumatoid Arthritis

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ABSTRACT

Aim and objectives: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder. Metabolic disturbances including hyperinsulinemia, dyslipidemia and insulin resistance, are common features in the majority of PCOS women. Women with PCOS may also be at increased risk of vitamin D deficiency. Several studies have reported that lower vitamin D levels are associated with increased risk of insulin resistance and metabolic disturbance among women with PCOS . The objective of the study was to evaluate the relationship between vitamin D and oxidative stress in pcos with RA

Materials And Methods : The study includes 20 healthy control women, and 20 were with PCOS with rheumatoid arthritis .Total sample size was 40. Vitamin D total is estimated by chemiluminescent immunoassay and to assess oxidative stress, serum Malonyldialdehyde (MDA) was done by thiobarbituric acid method and antioxidant level was assessed by estimation of serum vitamin C by dinitrophenyl hydrazine method.

Results: There was a decrease of vitamin -D in PCOS with RA (30.5 ±1.6), when compared with control(59.8 ±2.8). It was statistically significant (P<0.001). There was a decrease in vitamin -C in PCOS with RA (0.7 ±0.07) when compared with controls(1.1± 0.08). It was statistically significant (P<0.001). There was a increase of MDA in PCOS with RA, (9.0± 0.6) when compared with control (3.8± 0.2). It was statistically significant (P<0.001).

Conclusion: Low levels of Vitamin D deficiency in PCOS with RA patients is associated with inflammation which leads to Increased oxidative stress status , which may lead to connective tissue degradation leading to joint and periarticular deformities in rheumatoid arthritis.

KEYWORDS: Rheumatoid arthritis, oxidativestress, vitamin -D

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder, affecting women approximately 4%–18% at reproductive age. It is a heterogeneous disorder with different degrees of metabolic and reproductive dysfunctions. Metabolic disturbances including hyperinsulinemia ,dyslipidemia and insulin resistance, are common features in the majority of PCOS women. Women with PCOS may also be at increased risk of vitamin D deficiency (VDD) [(1)] . Several studies have reported that lower vitamin D levels are associated with increased risk of insulin resistance and metabolic disturbance among women with PCOS [(2)] . Recent studies suggest that oxidative stress may play a major role in the pathophysiology of polycystic ovary syndrome (PCOS). Rheumatoid arthritis (RA) is a chronic, multisystem disease with an unknown etiology affecting about 1 per cent of the world's population [(3).] RA is characterized by persistent inflammation in the synovial membranes of joints, associated with migration of activated phagocytes and other leukocytes into synovial and periarticular tissue [(4)] Formation of reactive oxygen species and lipid peroxides as a result of disease activity may play an important role in RA. While lowered concentrations of antioxidants in the blood considerably increase the probability of the occurrence of RA. Oxidative stress generated within an inflammatory joint can produce autoimmune phenomena and connective tissue destruction in rheumatoid synovitis [(5).] Oxygen free radicals have been implicated as mediators of tissue damage in women with RA. The objective of the study was to evaluate the relationship between vitamin D and oxidative stress in pcos with RA.

MATERIALS AND METHODS

The study was conducted at Rajiv Gandhi Institute of Medical Sciences srikakulam. Sampling design is

prospective, cross-sectional and comparative study. After obtaining institutional ethics approval the study was initiated in the month of April 2014 and ended in March 2015. During this study duration as per the inclusion and exclusion criteria the participants were selected. The written informed consent was obtained from participants and controls. The following were included in the present study PCOS participants were selected based on observation of oligoamenorrhea/ anovulation, clinical or biochemical evidence of hyperandrogenism and/or polycystic ovaries on ultrasonography. The diagnosis of PCOS was based on the ESHRE/ASRM consensus conference held in Rotterdam in 2003. Individuals with diabetes mellitus, thyroid dysfunction, cushing's syndrome, congenital and renal hyperplasia, hyperproloctinemia, androgen secreting tumour, renal and liver disorders, women with medication like ovaluation induction agent, antiandrogens, antidiabetic, antiobesity, hormonal drugs and current or previous use within last 6 month, smoking and alcohol intake were excluded from the study. The sample size was 20 healthy control women, and 20 were with PCOS with rheumatoid arthritis .Total sample size was 40.

Blood Sample collection: 5 ML of blood sample was obtained from the participants under all aseptic precautions after 12 hours of fasting. 2mL is transferred to EDTA and remaining blood in plain tubes. It was allowed to clot and centrifuged at 2000rpm for 10 minutes to obtain serum.

Biochemical Parameters: Plasma vitamin-D was measured by chemiluminescence immunoassay (CLIA) using commercially available kits. Oxidative stress was measured by estimating vitamin-C as antioxidant by 2, 4-dinitrophenyl hydrazine (DNPH) method. Ascorbic acid in plasma is oxidized by Cu^{+2} to form dehydro ascorbic acid which reacts with acidic 2,4-Dinitrophenyl hydrazine to form a red bis – hydrazone which is measured at A 520nm and malandialdehyde (MDA) as oxidant which is most commonly measured by a thiobarbituric acid-reactive substances (TBARS) assay with a simple spectrophotometric method. The amount of MDA corresponds to the chromogen found from MDA and thiobarbituric acid (TBA) with a maximum absorption at 532-535 nm.

RESULTS

The mean of vitamin -D of controls was 30.8 ng/mL. There was a decrease of 48.9% in vitamin -D in PCOS with RA, when compared with control. It was statistically significant (P<0.001). Compared to the control group, PCOS+RA group showed a statistically significant decrease in vitamin -D. The mean of vitamin -C of control was 0.8 mg/dL. There was a decrease 36.3% in vitamin -C in PCOS with RA , when compared with controls. It was statistically significant (P<0.001). The mean of MDA of controls was 3.8 mmol/L. There was a increase of 136.8% in MDA in PCOS with RA, when compared with control. It was statistically significant (P<0.001).

DISCUSSION

Some evidences suggest that vitamin D deficiency is one of the cause involved in the pathogenesis of metabolic syndrome in PCOS. The effects of vitamin D are mediated through both cellular and genetic 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. [(6)] Vitamin D, acts as a pro hormone, which play potential immune-suppressive roles and to exert an endocrine action on the immune system cells, generating anti-inflammatory and immunoregulatory effects [(7).] Tumour necrosis factor (TNF-α), Interleukin 1 (IL-1), and interleukin 6 (IL-6) play an important role in mediating this process. One of the important mechanisms of RA pathophysiology is the imbalance between Th1 and Th2 response with Th1 predominance (interleukin 2 and interferon γ excretion). The risk factors involve in RA development are the combination of genetic and environmental components. The most important genetic factor is associated with the major histocompatibility complex antigen HLA-DRB1 and shared epitope, which is closely related to serum presence of rheumatoid factor (RF) or anti-citrullinated peptide antibodies (a-CCP) [(8).] The environmental factor that contribute, is smoking, which can interact with genes to increase disease susceptibility [(9).] One of the other possible environmental factors is vitamin D. Despite being a crucial element of bone mineralization and calcium homeostasis, vitamin D also plays an important role in immune system. Active metabolite of vitamin D, calcitriol (1,25-dihydroxyvitamin D) can inhibit the macrophage synthesis of interleukines 1, 6, 12 and TNF-α, suppress the interleukin 2 secretion by Th1 lymphocytes and decrease antigen-presenting activity of macrophages – therefore restoring balance between Th1, Th17 and Th2 cells [(10).] calcitriol inhibits B-cell proliferation and plasma-cell differentiation . Vitamin D deficiency is more common in auto immunological diseases present in general population .

Increase in MDA levels could be due to increased generation of Reactive Oxygen Species (ROS), which led to excessive oxidative damage to the cell. The cause of increase production of ROS in PCOD is due to: PCOD is characterized by insulin resistance. Insulin resistance further leads to oxidative stress. Increased production of inflammatory markers like TNF –α and NF-Kappa B from the damaged cells. TNF- α is known mediator of insulin resistance which further aggravates the state of hyperglycemia and hyperinsulinemia. NFKappa B is an inflammatory transcription factor which leads to increase in the inflammatory state [(11)] .Sabuncu et al, [(11)]2001 compared PCOS with BMI and age-matched controls. They demonstrated that higher levels of erythrocyte MDA were seen in PCOS women compared with controls. Zhang et al [(12)](2008) demonstrated that serum MDA levels in PCOS women were significantly higher than those of controls

Ascorbic acid is a redox catalyst which can reduce,

and thereby neutralize, reactive oxygen species such as hydrogen peroxide. When the capacity of ascorbic acid is exceeded, free radicals can then diffuse and oxidize proteins. Vitamin C functions as an "electron sink", as it donates its electrons to the free radical species, thereby converting it to less harmful forms. Reduced ascorbic acid is the biologic labile form of vitamin C. It functions as an antioxidant . Replenishment of reduced ascorbic acid is facilitated by reduced Glutathione (GSH) which is another potent water soluble antioxidant. An overall depletion of antioxidants in hyperoxidant stress hampers the recycling of the oxidized form to the reduced form of ascorbic acid. [13]

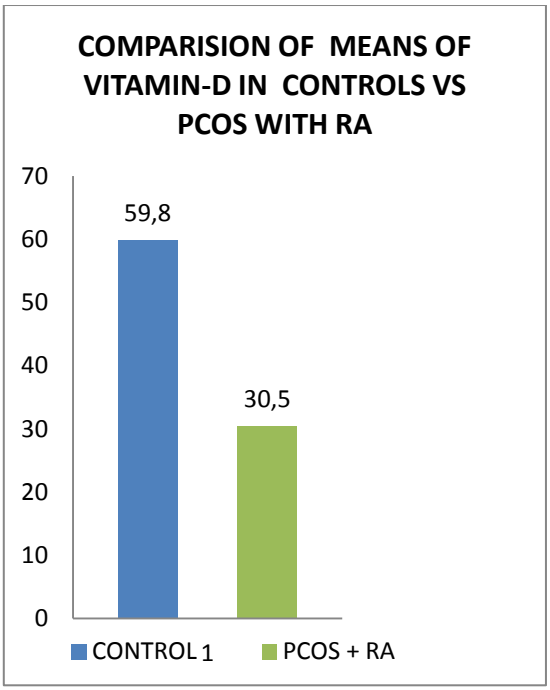
In this study, parameters such as plasma MDA as a marker of free radical mediated tissue destruction, vitamin C, as antioxidant were assayed to gain the oxidative stress status. MDA levels were found to be significantly elevated in the PCOS+RA compared to the controls. This is in agreement with other studies where higher MDA levels have been reported in individuals with RA [14]. Akyol in 2001 reported higher MDA levels in women with RA. MDA, the product of lipid peroxidation reacts with lysine residues in protein to produce immunogenic molecules, which can exacerbate inflammation. The longer chain polyunsaturated fatty acids are especially potent at increasing lipid peroxidation and causing cell damage by oxidative stress [15].

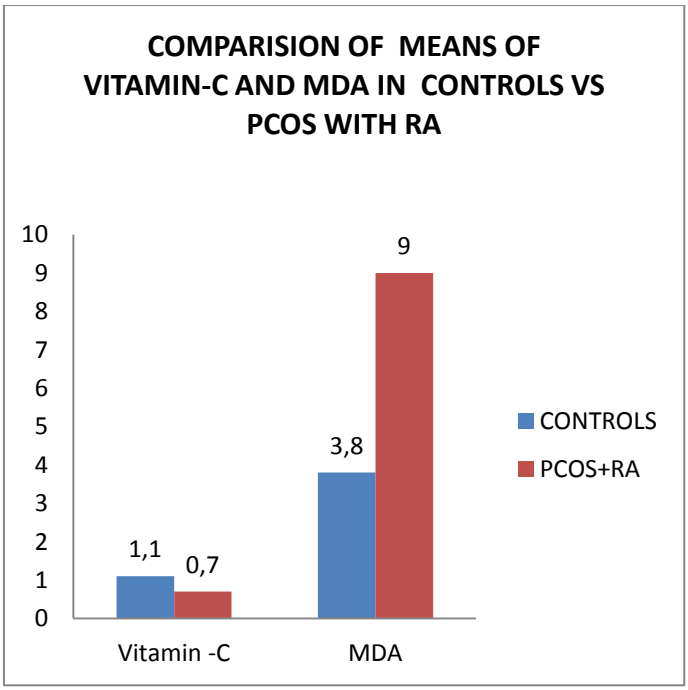
In this study significantly lower antioxidant vitamin C levels in PCOS+RA compared to the controls. In women with PCOS +RA insulin resistance is the factor for the presence of a chronic proinflammatory state[17]. In the general population TNF-α production is increased under chronic hyperglycemia and TNF- α has negative effect on insulin sensitivity [18].TNF- α is also an important mediator of insulin resistance in obesity and diabetes. Vitamin D deficiency is common in PCOS women and is associated with many symptoms, including infertility, CVD risk factors, insulin resistance and hirsutism. Previous evidence shows that vitamin D deficiency may be one of the factor in the pathogenesis of insulin resistance and PCOS.

This study showed that there was an alteration in the oxidant –antioxidant that is presence of oxidative stress in females having polycystic ovarian disease with rheumatoid arthritis . This oxidative stress may lead to complication of disease like infertility as well as other systemic disorders e.g. diabetes mellitus, cardiovascular dysfunction, dislipidemia and endometrial carcinoma. Antioxidants can be of help to fight against these free radicals. Increased oxidative stress in PCOS with rheumatoid arthritis is due to raised lipid peroxides, MDA and decreased vitamin C levels.

Comparison of parameters with mean and SEM				
PARAMETERS	GROUP NAME	N	MEAN	SEM
Vitamin -C	CONTROL	20	1.1	0.08
	PCOS + RA	20	0.7	0.07
MDA	CONTROL	20	3.8	0.2
	PCOS + RA	20	9.0	0.6
Vitamin-D	CONTROL	20	59.8	2.8
	PCOS + RA	20	30.5	1.6

Correlation of parameters vitamin –D with vitamin –C, MDA				
Si.no	Variable-1	Variable-2	r	p
1	vitamin –D	vitamin -C	0.319	<0.001
2	vitamin –D	MDA	-0.551	<0.001





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