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CORRELATION BETWEEN THE PREVALANCE OF LOW LEVELS OF SERUM VITAMIN D IN PATIENTS OF RHEUMATOID ARTHRITIS COMPARED TO HEALTHY CONTROLS

General Medicine

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ABSTRACT

Background : To examine the potential association of vitamin D levels in development of RA and its severity, a study is being conducted to find out vitamin D levels in patients of RA in comparison to healthy controls and to find out correlation between rheumatoid arthritis and serum vitamin D level.

Material and Methods : This cross sectional study was conducted at Narayan Medical College, Jamuhar, Sasaram. Bihar to find out the prevalence of vitamin D deficiency in Rheumatoid arthritis patients by analysis of serum vitamin D levels.

Results : This study was a cross sectional study, conducted at a tertiary care hospital. Fifty patients of rheumatoid arthritis diagnosed according to the 1987 revised criteria of rheumatology were included in this study. Patients diagnosed with RA for more than a year, those having chronic renal failure, systemic lupus erythematosus, diabetes , any systemic illness and patients on enzyme inducer drugs or on calcium and vitamin D supplements were excluded from this study. Fifty healthy control subjects were selected from general population who were age and sex matched and were free from any systemic illness. We have compared the serum vitamin 25 hydroxy vitamin D3 levels among rheumatoid arthritis patients and healthy controls.

Conclusion: Patients of RA, are at higher risk of falls and fractures by virtue of age and gender. The patient group who may benefit most from correction of vitamin D deficiency are older, post-menopausal and those with little or no sunlight exposure, non-white skin, individuals with malabsorption.

KEYWORDS

INTRODUCTION

Rheumatoid arthritis (RA) is a complex systemic autoimmune disease that predominantly targets synovial joints, especially small joints of hands and feet, and is characterized by joint destruction and chronic disability. Although the etiology of RA is unknown, various studies suggest that many environmental and genetic factors are responsible for development of RA. A recent study showed the association of dietary and supplemental vitamin D with RA incidence, higher intake of vitamin D was inversely associated with risk of RA. These immunomodulatory activities of vitamin D might be particularly efficient in RA patients and support a therapeutic role of 1,25 $(OH)_2$ D3 in such a disease.

Vitamin D is a fat soluble vitamin. Main source of vitamin D is de novo synthesis in the skin by ultraviolet B rays of sunlight. This depends on multiple factors like latitude, duration and time of sunlight exposure, atmospheric pollution, clothing and skin pigmentation. Worldwide one billion people are estimated to have vitamin D deficiency or insufficiency. Deficiency of vitamin D in India is very common (50-90%) in all age groups and both the sexes. More than ninety percent individuals above 50 year have vitamin D deficiency in India. 1,25-Dihydroxy vitamin D3 [1,25 $(OH)_2$ D3] the active metabolite of vitamin D3, is regulator of bone and calcium metabolism. It also exerts immunomodulation via the nuclear vitamin D Receptor (VDR) expressed in antigen-presenting cells (APC) and activated T/B cells. Main target of vitamin D immunomodulation are the dendritic cells (DCs) as indicated by inhibition of DC differentiation and maturation. This ultimately leads to vitamin D induced inhibition of DC-dependent T-cell activation. VDR agonists also inhibits the T-cell production of IL-17 which is a pro-inflammatory cytokine produced by Th17 cells in models of organ-specific autoimmunity in the brain, synovium, heart, and intestines. The net effect of the vitamin D is an enhancement of innate immunity with multifaceted regulation of adaptive immunity. There is increasing epidemiological evidence linking vitamin D deficiency and auto immune diseases including multiple sclerosis, rheumatoid arthritis, diabetes mellitus, inflammatory bowel disease and systemic lupus erythematosus. Reports of low serum vitamin D predicting development of autoimmune disease in future have been published for Multiple sclerosis, autoimmune DM and RA.

To examine the potential association of vitamin D levels in development of RA and its severity, a study is being conducted to find out vitamin D levels in patients of RA in comparison to healthy controls and to find out correlation between rheumatoid arthritis and serum vitamin D level.

AIMS AND OBJECTIVES

To study the prevalence of low levels of serum vitamin D in patients with rheumatoid arthritis as compared to healthy controls.

MATERIALS AND METHODS:

Study design: It is a cross sectional study to find out the prevalence of vitamin D deficiency in Rheumatoid arthritis patients by analysis of serum vitamin Dlevels.

Study place: Medicine Department of Narayan Medical College, Jamuhar, Sasaram, Bihar.

Inclusion criteria:

- Diagnosed patients of Rheumatoid Arthritis with age more than 30 years including both males and females [IPD and OPD].

Exclusion criteria:

- Patients not having Rheumatoid arthritis (RA).
- Patients diagnosed with RA for more than a year.
- Patients of RA having chronic renal failure, Systemic lupus erythematosus, Diabetes mellitus, any systemic illness and patients on enzyme inducer drugs or on calcium and vitamin D supplements.
- Patients not willing to take part in the study.

Statistical Analysis:

Methodology: Fifty patients of rheumatoid arthritis were diagnosed according to the revised criteria of the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) 2010 were included in the study. Fifty healthy control subjects were selected from general population whose age and sex matched and free from any disease. Written informed consent were taken from all the eligible patients. Laboratory diagnosis of RA

patients were done using Anti CCP. ESR were measured by Westergren method. C-reactive protein (CRP) were also measured, value more than 3ng/ml were considered positive. Serum 25 (OH) Vitamin D levels measured by enzyme linked immuno sorbent assay (ELISA) kit. . Vitamin D deficiency were defined as 25 (OH) vitamin D level below 25 nmol/l (10 ng/ml), vitamin D insufficiency were defined as 25 (OH) vitamin D level 25-75 nmol/l (10 - 30 ng/ml) and vitamin D sufficiency were defined as 25 (OH) vitamin D level 75-250 nmol/l (30 - 100 ng/ml).

RESULT AND DISCUSSION :

The mean age of the patients in RA group was 48.22 ± 8.961 years and in the control group was 46.66 ± 6.137 years in our study. Thus, both the groups were comparable at baseline with respect to age. According to Harrison Principles of internal medicine 18 edition, RA is more common between 25-55 years of age. Also in our study patients fall in to this age group. Another study conducted by Rajeev Sharma et al[163] showed that mean age of case and control was 40.9750 and 42.6375 and was comparable with our study. In a study conducted by Maurizio et al, the mean age was found to be 58.9 ± 1.1 years and the probable reason for this high mean age could be their inclusion criteria of enrolling all the patients of RA with age ≤ 75. M cutolo et al included female RA patients from north and south Europe were compared with healthy controls of same age. The mean age of RA patients from north Europe was 58.5 ± 1.1 and among south Europe was 56.3 ± 2.3 and controls was 59.9 ± 0.9 and 51 ± 3.8 respectively. Higher mean age of presentation of patients of RA in European countries could be attributed to some genetic/environmental factors which can be a topic of further investigation in Indian population. It has also been noted that the incidence of RA is more in European countries as compared to Indian subcontinent.

Rheumatoid arthritis occurs more commonly in females than in males, with a 2–3:1 ratio. Interestingly, studies of RA from some of the Latin American and African countries show an even greater predominance of disease in females compared to males, with ratios of 6–8:1. Study conducted by Maurizio Rossini et al. obtained results showing major proportion of patients having RA were females (85%) with only 15% patients being males. Gender wise distribution of patients in our study showed that number of females with RA were 40 (80%) and number of males were 10 (20%). Also the incidence of RA in our study in the age group of below 50 years was 3 times more common among the females and over 50 years of age it was 6-7 times more common in the females. This shows that the incidence among our patient population increased with the age of the patients. From the literature it is evident that the incidence of RA is more in female population which is reflecting in our study as well.

The mean hemoglobin in RA group in our study was found to be 11.48 ± 0.89 gm/dl and for control group 12.568 ± 1.121 gm/dl. In the study conducted by Sharma et al, the mean hemoglobin levels among RA and control group were 10.5788 ± 2.19 gm/dl and 11.96 ± 1.37 gm/dl respectively. Furst et al in their study observed that the proportion of patients having low Hb were 16.7% and 83.3% had normal Hb levels. More patients in the low± Hb group had a history of comorbid cardiovascular disease, diabetes, and gastrointestinal disease. Despite changes in treatment paradigms, low Hb levels remain prevalent in RA patients. Hence the authors concluded that low Hb levels may be associated with RA disease severity and the presence of certain comorbidities. However in our study, based on the inclusion criteria it can be assumed that the low levels of Hb were due to RA disease itself.

The mean value of platelet count in RA patients in our study was 2.454 ± 0.64 cmm and control group was 3.2 ± 3.81/ cmm. Sharma et al in their study found that mean value of platelet was 2.63 ± 1.09 and 2.64 ± 0.92 among the case and control respectively. Hutchinson et al, in their study of 75 patients with rheumatoid arthritis, observed that 39 (52%) had thrombocytosis and 36 (48%) normal platelet count. Hence the authors concluded that there is a significant relationship between the platelet count and disease severity and an inverse correlation with level of hemoglobin. As from the above figures it is clear that the patients in our study had normal platelet count and the reason for such finding could be due to exclusion of patients with active disease.

Mean ESR of RA patients in our study was 78.4 ± 28.7 mm/ first hour and of the control group was 19.2 ± 17.33 mm/first hour. Sharma et al reported the ESR of the patients in their study 40.96 ± 27.14 mm/first hour and for the control group 19.06 ± 5.042 mm/first hour. Ifigenia kotsoglou et al observed the value of ESR was 38.0 ± 4.6 mm/h (mean ± SEM) in the group of patients with RA. In our study the ESR of the patients were on the higher as compared to the above study. The reason for such a finding could be due to active disease which was not considered as a variable of our study.

CRP

In our study of, CRP was higher in RF positive patients (64.70%) as compared to RF negative patients(43.80%).On applying Chi square test it was found that the p value was not significant. On evaluation of CRP with Vitamin D3 levels it was observed that, it shared an inverse relation. The mean vitamin D3 levels among CRP positive and negative patients were 14.71 ± 3.06 and 15.93 ± 4.06.

Ifigenia kotsoglou et al in their study found that the mean CRP was 7.6 ± 1.57 mg/litre (mean ± SEM) (normal values < 3 mg/litre).

The mean serum calcium level was lower among RA group (7.826 ± 0.910) compared to control group (9.016 ± 0.942). Also, on categorizing patients of RA into RF positive and negative, the mean serum calcium levels obtained were 7.68 ± 0.81 and 8.14 ± 1.06 respectively. On comparing the serum calcium levels in relation to sex it was found that the mean serum calcium was lower in females (7.72 ± 0.961) in comparison to males (8.23 ± 0.529) and the p value was statistically significant <0.035 after applying unpaired t test. Sharma et al in their study observed that the mean serum calcium among the case 8.19 ± 0.579 and in the control group 8.515 ± 0.869. Scott DL et al in their study concluded that serum calcium levels are lower in disease than in health, and this occurs in RA as well as other diseases. The low serum calcium levels in RA patients could be attributed to active disease.

In our study the mean vitamin D3 levels among RA patients were 15.22 ± 3.53 and among the controls was 30.8 ± 8.74. Using unpaired t test the p value was found to be statistically significant. On gender wise distribution of RA patients the mean vitamin D3 levels among females was 14.98 ± 3.39 and males being 16.18 ± 4.08. On applying unpaired t test p value was not found to be significant. On deriving a correlation between serum calcium and vitamin D3 levels, the p value was found to be statistically significant by Pearson's correlation co-efficient. Sharma et al found that Vitamin D levels in high disease activity group was significantly low compared to vitamin D level in patients with low and moderate disease activity (p<.001). M Cutolo et al in his study reported no significant difference between vitamin D3 levels among RA and control groups. However on further evaluation they reported that 25 (OH) D values showed a significant correlation (negative) with RA clinical status (DAS 28) in both north and south European RA patients suggesting possible effects of vitamin D among other factors on disease activity. Maurizio et al in their study found that vitamin D3 deficiency is quite common in RA patients, but there was a negative correlation with disease activity and disability score.

Hence in the above mentioned studies the authors reported that vitamin D3 levels were low in both RA and control group. Also on analysis, vitamin D had negative correlation with disease activity among RA patients. However in our study the relationship between the disease activity and vitamin D3 levels could not be established as it was not studied but it is indicated from the above studies that the low serum vitamin D3 could be due to active disease.

Ifigenia et al in their study found that vitamin D levels were found to be low in a group of patients with RA as compared to control group. Vitamin D levels were found to be negatively correlated with disease activity. Nashwa et al in their study found that 25(OH) D_3 deficiency was similar in both RA patients and controls. Although, the mean serum 25(OH) D_3 level was less among RA patients than among controls but there was no statistical significant difference. However, vitamin D3 deficiency was significantly correlated with increased disease activity and disability but not with BMD. In our study on correlation between vitamin D3 and BMD it was found that mean vitamin D3 in patients having osteopenia and osteoporosis were 15.03 ± 3.43 and 16.22±2.32 respectively. On application of one way ANOVA-F the p value obtained was not significant. Kerr S et al in their study, which included RA males only, found that the prevalence of 25-OH-D insufficiency and deficiency were 84% and 43%, respectively. Also it was found that both insufficiency and deficiency were more common with anti-cyclic citrullinated peptide antibody positivity and in the absence of vitamin D supplementation.

The value of mean anti-ccp in our study was higher among RA females than among RA males 189.5 ± 36.12 and 168.8 ± 28.51 respectively. Using unpaired t test the p value was not significant. The mean anti-ccp level was higher among RA factor positive (181.07 ± 36.28) as compared to RA factor negative (194.6 ± 32.85). On analysis using unpaired t test p value was not significant.

CONCLUSION :

In our study it has been observed that vitamin D deficiency and insufficiency is common in rheumatoid arthritis patients in comparision to healthy controls.

Patients of RA, are at higher risk of falls and fractures by virtue of age and gender. The patient group who may benefit most from correction of vitamin D deficiency are older, post-menopausal and those with little or no sunlight exposure, non-white skin, individuals with malabsorption.

Hence it is essential that all the patients having rheumatoid arthritis can be given vitamin D3 supplementation for prevention of musculoskeletal pain relief and osteoporosis.

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