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The relationship between serum 25(OH) D3 and risk of musculoskeletal infection: results from prospective case-control study

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Abstract

Introduction: Interaction with the immune system is one of the most recently established nonclassic effects of vitamin D. Crucially, these effects seem to be mediated not only by the endocrine function of circulating calcitriol but also via paracrine and/or intracrine activity of 1,25 (OH)2D3 from its precursor 25(OH)D3, the main circulating metabolite of VitD. The ability of this vitamin to influence human immune responsiveness seems to be highly dependent on the 25(OH)D3 status of individuals and may lead to aberrant response to infection in those who are lacking VitD.

Methods: 70 patients presenting to Orthopaedic OPD chosen randomly by closed envelope method and 50 patients with musculoskeletal infections were selected and there serum 25-hydroxyvitamin D3 levels were measured.

Results: 64% cases had 25-hydroxyvitamin D3 deficiency in comparison to 39% in controls. P value = 0.015, Odds ratio = 2.779, Confidence interval (95%) – lower limit 1.215, upper limit 6.254

Conclusion: VitD deficiency increases susceptibility to musculoskeletal infections and musculoskeletal infections are common cause of morbidity and mortality

among orthopaedic patients, especially in developing countries.

Keywords: OH)2D3, VitD, Healthy

Introduction

Vitamin D is a vitamin with hormone-like activity that regulates the functions of over 200 genes and is essential for growth and development of the body. Vitamin D deficiency is widely prevalent throughout the world. Over the past few years, resurgence in vitamin D deficiency and nutritional rickets has been reported throughout the world. Studies have shown that as much as 69%-82% of the population in India has vitamin D levels in plasma less than the minimum acceptable limit.[4] In different studies in North India 96% of neonates,[5] 91% of healthy school girls,[6] 78% of healthy hospital staff,[1] and 84% of pregnant women[5] were found to have hypovitaminosis D. The major source of vitamin D for children and adults is exposure to natural sunlight. Very few foods naturally contain or are fortified with vitamin D. Thus, the major cause of vitamin D deficiency is inadequate exposure to sunlight.1,25(OH)2 Vit D has a wide range of biological actions, including inhibiting cellular proliferation and inducing terminal differentiation, inhibiting angiogenesis, stimulating insulin production, inhibiting renin production, and stimulating macrophage cathelicidin production. Also Vitamin D is an important regulator of immune system. It is well established that immune cells can produce the hormonally active metabolite of vitamin D. Studies have shown that children with rickets have reduced number of peripheral T-lymphocytes, defective neutrophil motility and reduced phagocytic activity against bacteria.[7-9] Inadequate serum vitamin D levels have been found to be associated many infectious diseases. The prototypical example of a connection between vitamin D insufficiency and susceptibility to infectious disease is tuberculosis. There are also many studies in which association has been found between vitamin D deficiency and viral or respiratory tract infections. As per our knowledge and literatre available, till now no study has been done to study role of vitamin D in musculoskeletal infections. So we conducted this study to calculate the proportion of vitamin D deficiency in patients presenting with musculoskeletal infections.

Material and Methods

A hospital based case-control study was conducted at the Central Institute of Orthopaedics in collaboration with the Department of Biochemistry at Vardhman Mahavir Medical College & Safdarjung hospital. The study was conducted for duration of one and half year from October 2015 to April 2018. Cases werepatients with musculoskeletal infectionsadmitted as in-patients or seen in the outpatient department.Patients with any of the following musculoskeletal infections i.e. Soft tissue infection, Septic arthritis, Tubercular arthritis, Acute Osteomyelitis, Chronic Osteomyelitis, Tubercular Osteomyelitis, Spinal tuberculosis, Post-operative infection etc were included in the study. Patients who were immunocompromised or who hadopen fracture, liver , GI tract or renal disease were excluded from study. Controls were patients presenting to Orthopaedic OPD with complaint other then musculoskeletal infection and they were chosen randomly by closed envelope method.

All the patients included in the study after initial evaluations were subjected for serum 25-hydroxy vitamin D3 concentration measurement.Fasting blood samples of all the patients included in study were taken and serum 25-hydroxy vitamin D3 levels were measured by ELISA method.Reference range taken wasdeficiency

- <20 ng/ml, suboptimal – 20-30 ng/ml, optimal – 30- 70 ng/ml, overdose – 70-150 ng/ml, toxicity - >150 ng/ml.

Data were analysed using SPSS (IBM SPSS Statistics 20). Standard statistical tests were used including odds ratios and binary logistic regression.

Observations and Results

66 patients presenting to Orthopaedic outpatient clinic chosen randomly by closed envelope method were enrolled as controls and 50 patients with musculoskeletal infections were enrolled as cases in our study and following observations were made. The mean age in control group was 30 years with standard deviation of 18 years ranging from 3 to 70 years, whereas mean age in case group was 26 years with standard deviation of 14 years ranging from 4 to 64 years. There were 33 males and 17 females among cases whereas there were 44 males and 22 females among control group. Among cases, 11 were suffering from Chronic Osteomyelitis, 11 from Pott's Spine, 20 from Post operative infection, 6 from Septic arthritis and 2 from Tubercular synovitis.Among controls, 21 were suffering from Soft tissue injury, 9 from Backache, 24 from Traumatic fracture and 12 from Osteoarthritis. The mean Vit D3 level in cases was 25.4 ng/ml with standard deviation of 23.8. Range of serum Vit D3 levels in cases was from 2 to 130. Whereasmean Vit D3 level in control group was 28.5 ng/ml with standard deviation of 16.2. Range of serum Vit D3 levels in controls was from 6 to 85.

Comparison of Vit D3 status among cases and controls was done by applying binary logistic regression and results were as follows:

P value = 0.015, Odds ratio = 2.779, Confidence interval (95%) – lower limit 1.215, upper limit 6.254.

P value of 0.015 is lesser than 0.05 suggesting it to be significant. Also odds ratio calculated comes out to be 2.779 which is more than 1.

	Serum Vit D3		Total
	Deficiency/Insufficiency	Optimal	
Cases	39	11	50
Controls	37	29	66
Total	76	40	116

Discussion

The past few years have witnessed a remarkable renaissance in vitamin D research and a complete re-evaluation of its benefits to human health. Two key factors have catalyzed these changes. The first stems from our new perspective on what constitutes optimal vitamin D status. Until 10 years ago, vitamin D deficiency was primarily defined by the presence or absence of rickets or the adult form of this disease, osteomalacia. In this setting, serum concentrations of the main circulating form of vitamin D (25-hydroxyvitamin D) of <10–15 nmol/l were considered to indicate vitamin D deficiency. Although values higher than 10–15 nmol/l were generally considered to be normal, a variety of reports over the past decade have challenged this perception. Specifically, studies of serum parathyroid hormone levels and intestinal calcium uptake in humans have shown continuing changes in these parameters with serum concentrations of 25-hydroxyvitamin D up to 80 nmol/l.[10,11]

The overarching conclusion from these studies is that optimal vitamin D status cannot simply be defined by the diagnosis of rachitic bone disease, but is more probably represented by a target serum level of 25-hydroxyvitamin D of ~75 nmol/l (or 30 ng/ml). As a consequence of this observation, a new term "vitamin D insufficiency" has been coined to describe individuals

with suboptimal levels of serum 25-hydroxyvitamin D (<75 nmol/l) who are asymptomatic for rachitic bone disease.[12]Debate continues concerning many of the parameters associated with the interpretation and treatment of vitamin D insufficiency. Notable examples include the point at which vitamin D insufficiency transitions into vitamin D deficiency, and whether the target optimal dose for 25-hydroxyvitamin D status may in some settings be higher than 75 nmol/l.[13]However, irrespective of these issues, a considerable proportion of the worldwide population probably have suboptimal vitamin D status.[14,15]Awareness of this public health problem has underpinned the second surge in vitamin D research aimed at defining the consequences of vitamin D insufficiency with respect to human health.

Non classical effects of vitamin D, namely those beyond its established actions on calcium homeostasis and bone metabolism, have been recognized for a quarter of a century and include anticancer and immunomodulatory responses. These responses were initially considered to be novel side effects secondary to the classical effects of vitamin D that could be targeted via therapeutic use of the active form of vitamin D (1,25-dihydroxyvitamin D) or less calcemic analogs of 1,25-dihydroxyvitamin D.The vitamin-D-activating enzyme 25-hydroxyvitamin D-1α-hydroxylase (encoded by the gene CYP27B1) is, however, expressed by many peripheral tissues including those of the immune system. This fact suggests that in normal physiology, local concentrations of 1,25-dihydroxyvitamin D may be highly dependent on the bioavailability of substrates 25-hydroxyvitamin D, in other words vitamin D status.

The physiological importance of local synthesis of 1,25-dihydroxyvitamin D is most clearly illustrated by the interaction between vitamin D and the immune system. These studies have revealed potent effects of vitamin D on T-cell and B-cell adaptive immunity, but many of the most prominent advances in the past few years have focused on the ability of vitamin D to promote innate antimicrobial responses. Compelling evidence from in vitro experiments demonstrates that vitamin D can act as a potent stimulator of innate antimicrobial responses and this evidence is supported by association studies that link vitamin D insufficiency with increased risk or severity of infection.

Studies have shown that serum levels of 25(OH)D3 below 30 ng/mL (i.e., 75 nmol/L) seem to play a role in TB prevalence and susceptibility to active disease.[16] The incidence of virus infection typically peaks in the winter months when cutaneous VitD synthesis is lower.[17]Indeed, recent epidemiological evidence suggests that throughout the world influenza infection also occurs mainly during the month following the winter solstice, when circulating 25(OH) Vit D3 levels reach the nadir.[18] In children with inadequate serum levels, infections seem particularly of viral origin. Concordantly, several studies have pointed out to the potential protective role of adequate serum 25(OH) Vit D3 concentrations against influenza and RSV infections.[19] While 25(OH) Vit D3 and 1,25(OH)2 Vit D3 related pathways have been mainly studied in relation to the host response to influenza infections, they interestingly seem to play a role in the control of HIV infection as well. Indeed, an increased prevalence of VitD deficiency in HIV-infected individuals has been noted in comparison with uninfected hosts.[20]More interestingly, shorter survival times were associated with abnormally low serum calcitriol while positive impacts on the CD4+ T-cell counts were observed after VitD supplementation.[21,22] These results indicate that serum

1,25 dihydroxy VitD3 is correlated with the degree of immune deficiency during HIV infection; low serum levels being associated with increased incidence of acquired immunodeficiency syndrome events.[23,24]

In our study also we have found the similar results that patients with musculoskeletal infections have lower mean serum levels of 25OH vitamin D3 than controls matched on sex and age.

These findings are important because they show that people with Vit D deficiency have increased risk of suffering from musculoskeletal infections and musculoskeletal infections are common cause of morbidity and mortality among orthopaedic patients, especially in developing countries.

Conclusion

This study has some shortcomings that limit the conclusions. The main weakness is the limited number of patients in both case and control groups. Also the effect of Vit D supplementation on musculoskeletal infections was not included in the study. Prospective studies to firmly establish the relationship between Vit D and musculoskeletal infections as well as evaluation of Vit D supplementation in musculoskeletal infections are needed.

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