



A SPECTRUM OF NON-SKELETAL DISEASES IN THE VITAMIN D DEFICIENT POPULATION OF WEST BENGAL

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ABSTRACT

Background: The extra osseous role of vitamin D in the pathogenesis of an array of several diseases like diabetes, hypertension, hypothyroid, CKD, CVD, cancer, autoimmune diseases have been in focus in the recent years. Keeping in compliance with the worldwide trend of vitamin D deficiency, various reports suggest 50-90% deficiency of vitamin D among Indians. Vitamin D receptors have been found in the tissues of breast, colon, lungs, immune cells which strongly indicates it as a predisposing factor for the associated diseases. The retrospective study focuses on the prevalence of various non-skeletal diseases in a large cohort of vitamin D deficient population of West Bengal.

Materials: A total of 1933 patients were included in the study from OPD and IPD of RKMS from Jan 2014 to Aug 2015. Patient details were obtained from the medical records section.

Results: 83.2% (1609/1933) patients were observed to be vitamin D deficient. Among them 247 patients had T2DM, 291 patients shows hypertension and 406 were found to be hypothyroids with mean vitamin D 12.5, 12.1 and 13.2 ng/ml respectively indicating severe vitamin D deficiency. Excluding these three prevalence of other sixteen major diseases were observed in this population accompanied with severe/insufficient vitamin D deficiency.

Conclusions: The protective role of vitamin D in non-skeletal and metabolic diseases should be highlighted in the awareness programs on serious consequences of asymptomatic vitamin D deficiency among all sections of the society including clinicians. The need of the hour is to initiate mass screening of vitamin D deficiency at the government level and supplementation via medication or vitamin D fortified food wherever it is required in order to prevent or delay the fatal outcome of it.

KEYWORDS : vitamin D deficiency, non-skeletal, diabetes, hypertension, hypothyroid

Introduction:

Vitamin D deficiency (VDD) is considered to be one of the most underappreciated medical conditions throughout the world. Vitamin D has been evolved as an active hormone due to its participation in the pathogenesis of many chronic diseases including autoimmune diseases, diabetes, hypertension, chronic kidney disease, malignancies, cardiovascular and infectious diseases apart from its traditional role in regulation of calcium and bone metabolism. Vitamin D deficiency has been reported worldwide (Alyahya, Lee et al., 2014; Vierucci, Del Pistoia et al., 2014; Oberg, Jorde et al., 2014; Eggemoen, Knutsen et al., 2013; Suzuki, Maruyama et al., 2014; Radhakishun, van Vliet et al., 2014) including India. 50- 90% of the Indian population is vitamin D deficient inspite of ample sunlight (Marwaha, Sripathy 2008) We reported a striking percentage (83.2%) of vitamin D deficiency among the Bengali population of Kolkata in our earlier study (Halder, Dastidar 2016).

In India prevalence of VDD is very common in all age groups including children and adolescents (Nair and Maseeh 2012), which might be attributed to dietary habits, indoor activities, use of sunscreen etc. Emerging evidences indicating the growing incidence of VDD in school going children is a major concern. VDD is thought to be a predisposing factor for many non-skeletal diseases including asthma, tuberculosis, gastrointestinal diseases, endocrine disorders, neurological disorders in addition to skeletal diseases. An inverse association of VDD with chronic liver diseases, diabetes, HTN are reported across the world (Forman, Giovannucci 2007). The presence of Vitamin D receptors (VDR) on various extra renal tissues like breast, colon, lungs, T and B lymphocytes strengthens association of VDD with these diseases. Recent research highlights the role of VDR polymorphisms in VDD emphasizing gene –environment interaction behind the chronic metabolic diseases.

There are several meta analysis and cross sectional studies which depicted the protective role of 1,25(OH)vitamin D in suppression of autoimmune disorders like type 1 diabetes, rheumatoid arthritis and Hashimoto's thyroiditis. Moreover the incidence of chronic lung disease, anaemia, prostatomegaly, PCOS, OSA increases with increased vitamin D deficiency which has been demonstrated in

multiple human and mouse model experiments. Current research in this field revealed that vitamin D supplementation could improve the clinical scenario of the diseases and might delay the occurrence of these diseases.

The importance of VDD in non skeletal diseases remain ignored by the clinicians in our country till date inspite of its pivotal role as an immunomodulator. Very few studies are reported on the VDD limiting extra skeletal diseases in India. The aim of our study is to highlight the coexistence of non-skeletal diseases and vitamin D deficiency in the Bengali population of West Bengal which has not been studied so far.

Material and Methods:

A total of 1933 patients who presented to the out-patient department (OPD) and in patient department (IPD) of Ramakrishna Mission Seva Pratishthan, Kolkata between January 2014 to August 2015 were screened for vitamin D deficiency. One thousand six hundred and nine persons who showed vitamin D deficiency were recruited for the study. Detailed medical histories, anthropometric measurements and laboratory findings were obtained from the record section of the hospital. Patients having various chronic diseases accompanied with vitamin D deficiency were further meticulously evaluated in consultation with the medical experts in respective departments. Serum 25(OH)vitamin D <20 ng/ml defined as deficiency and level (21-29) ng/ml was considered as insufficiency according to American society guidelines. This was followed to determine VDD among the patients

Result:

83.2% (1609/1933) of a total nineteen hundred and thirty three patients one thousand six hundred and nine persons were found to be vitamin D deficient. All the patients diagnosed with vitamin D deficiency and/or insufficiency were the local inhabitants of Kolkata, West Bengal. The mean age of the patients was 48.05±11.3 years. There were 603 males and 1303 females. Females showed much more deficiency than their male counterparts.

Our study showed that mean serum 25(OH)vitamin D was <20ng/ml in all the patients afflicted with various non skeletal diseases expecting

the two, cerebrovascular accident and gastritis with mean vitamin D 23.3 ng/ml and 22.3 ng/ml respectively which also showed insufficiency [Fig:1]

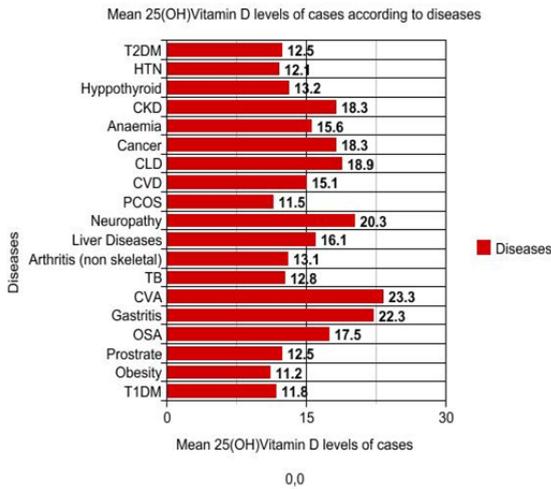


Fig 1: A comparison of mean serum 25(OH) vitamin D in various non-skeletal disease

In this large section of patients with hypovitaminosis D 247 had Type 2 Diabetes Mellitus, 291 had hypertension and 406 patients were found to be hypothyroids. Patients with chronic kidney disease and cardiovascular diseases were 149 and 155 respectively. Ninety- five patients showed neuropathy whereas chronic lung disease was found in ninety seven patients. A significant number (76) of various types of cancers were observed in this vitamin D deficient patient population. Apart from these 3.6% of the population suffered from non skeletal arthritis. Although incidence of tuberculosis, prostatomegaly and cerebro vascular accidents were found to be very low in the test group of the study [Table :I]

Table I: Distribution of various nonskeletal diseases accompanied with vitamin D deficiency

Diseases	Number (N)	(%)
Type 2 Diabetes Mellitus(T2DM)	247	15.3
Hypertension (HTN)	291	18.08
Hypothyroid	406	25.2
Chronic Kidney Disease (CKD)	149	9.26
Anaemia	46	2.8
Cancer	76	4.7
Chronic Lung Disease (CLD)	97	6.02
Cardiovascular Disease (CVD)	155	9.6
Polycystic Ovarian Syndrome (PCOS)	13	0.8
Neuropathy	95	5.9
Liver Diseases	50	3.1
Arthritis (other than skeletal)	58	3.6
Tuberculosis (TB)	21	1.3
Cerebrovascular Accident (CVA)	21	1.3
Gastritis	57	3.5
Obstructive Sleep Apnea (OSA)	37	2.2
Prostatomegaly	20	1.2
Obesity	39	2.4
Type 1 Diabetes Mellitus (T1DM)	54	3.35

Discussion:

A close association of Vitamin D deficiency with extra-skeletal disorders has been reported in numerous epidemiological studies which draws attention of the researchers and clinical scientists across the globe. The predisposing effect of serum vitamin D towards diabetes (Yingying, Ling 2009), hypertension (Li 2003), CKD (Jones 2007), CLD (Franco, Paz-Filho 2009), cancer (Feldman, Zhao 2009), polycystic ovarian syndrome (Wehr, Trummer 2011) and many other

metabolic diseases has been reported in various parts of the world. Apart from metabolic diseases the protective role of vitamin D is now been observed in auto immune disorders including type I diabetes, rheumatoid arthritis Hashimoto thyroiditis and multiple sclerosis (Holick 2004). Vitamin D has been accepted as an immuno modulator due to its profound impact on the pathophysiology of various extra skeletal diseases and it has been observed in some studies that with vitamin D supplementation the prognosis of the diseases could be improved. But it still remains a debatable issue due to some conflicting results which disapproves the former statement. A negative association of serum 25(OH) vitamin D with anti TPO has been demonstrated in the Bengali patients with Hashimoto thyroiditis in our early study (Halder, Dastidar et al 2016). We also carried out a pilot study which revealed that 24.3% of the vitamin D deficient population had type II diabetes, hypothyroidism and hypertension either individually or in combination (Halder, Dastidar 2016).

In this present study also higher prevalence of diabetes (15.3%), hypertension (18.8%) and hypothyroidism (25.2%) are noticed in vitamin D deficient Bengali population in comparison to other metabolic diseases.

The presence of vitamin D receptors on the extra renal tissues might indicate its influence over these diseases. Calcitriol stimulates insulin secretion after binding to its receptor on beta cells of the pancreas and eventually its' deficiency causes insulin resistance which is believed to be a prime cause of type II diabetes (Yingying, Ling 2009).The potential role of vitamin D in the regulation of blood pressure has been a well accepted phenomenon due to its negative influence on Renin Angiotensin System (RAAS) (Li 2003).Numerous epidemiological studies demonstrated an inverse relationship between hypovitaminosis D and hypothyroidism (Holick 2004) as vitamin D stimulates iodide uptake by the thyrocytes of thyroid gland. In addition to these, two most important chronic and debilitating diseases like CKD (chronic kidney disease) and CVD (cardio vascular disease) who are thought to be the major cause of death in coming years as predicted by World Health Organisation (WHO) predisposed by vitamin D deficiency. This study also reveals approximately ten percent of the vitamin D deficient people are suffering from either from CKDs or CVDs or from both which is quite alarming. Vitamin D has been emerged as a key player in the underlying pathology of metabolic syndrome, obesity and liver diseases (Gami, Witt 2007) and their close association has been reported in many human and mouse model experiments. Even various types of cancers including breast, colon, esophageal, ovary etc (4.5%) bear a significant correlation with vitamin D deficiency due to loss of anti proliferative activity of vitamin D and its active metabolites as obvious from our study 5.9% of the study population with hypovitaminosis D showed neuropathy symptoms highlighting the former's role on nervous system, neuro transmission and neuro immune modulation which has been demonstrated in various studies (McGrath, Feron 2001). A significant positive association of vitamin D deficiency with auto immune diseases like type I diabetes and hashimoto thyroiditis has been found in the present study as well as our earlier studies (Li 2003) which is in accord of other studies conducted in the other parts of the globe. In addition to these the crucial role of vitamin D has been elucidated in numerous nonskeletal diseases. Our present study shows that anemia (2.8%) (Dastidar and Halder 2015), cancer (4.7%), polycystic ovarian syndrome(0.8%), nonskeletal arthritis (3.6%) , chronic lung disease (6.02%), tuberculosis (1.3%), cerebrovascular accident (1.3%), gastritis (3.5%), obstructive sleep apnea (2.2%), obesity (2.4%), liver disease (3.1%), prostatomegaly (1.2%) etc (Espinosa, Esposito 2013) are accompanied with vitamin D deficiency.

There is indeed a dearth of clinical trials and related studies with vitamin D supplementations in extra skeletal diseases in spite of its enormous role in the immune pathology of these diseases but some researchers claimed that with timely and adequate supplementation with vitamin D prognosis of many life threatening diseases like CKD, CVD, neurological disorders could be improved (Zittermann 2006; Wang, Pencina 2008; Petchev, Johnson 2008; Eyles, Smith 2005).The incidence of tuberculosis, pneumonia and other chronic lung diseases could be reduced if vitamin D supplements are incorporated in the treatment regime (Ho-Pham, Nguyen 2010) as it enhances antimicrobial peptide production and regulates inflammatory responses. Sharma et al observed in their study that the clinical scenario of rheumatoid arthritis, a systematic, debilitating disease got improved with vitamin D therapy (Cutolo 2008) Along with the

positive association of vitamin D supplementation with metabolic diseases there are some studies which yielded conflicting results stating that the ineffectiveness of vitamin D supplementation (Gami, Witt 2007; Yingying, Ling 2009 ; Li 2003) in the prognosis of the diseases.

The effect of hypovitaminosis D in these chronic metabolic diseases remain totally unexplored in Eastern India with a special emphasis to Kolkata, West Bengal till date. From this present study it was observed that most of the chronic, life style disorders exist in this large number of vitamin D deficient patient population which again indicates the predisposing effect of vitamin D deficiency on chronic metabolic disorders. A quite obvious relationship between the two was observed in this study but which one predisposes the other was not clear. The large cohort of patients might be considered the strength of the study where as there is a limitation, since it is a hospital based study, so true picture of the society might not be reflected from this study.

Conclusion:

The status of vitamin D is still limited as a nutrient among the commoners though it has been recognized as a hormone long ago. A major section of the society is completely unaware of the serious consequences of vitamin D deficiency as it remains asymptomatic for prolonged period of time. Moreover measurement of serum 25 (OH)vitamin D is an expensive test and beyond the reach of the poor/lower middle class section of the society, which restrains the clinicians to prescribe vitamin D testing. Proper awareness of the protective role of vitamin D in various non-skeletal, metabolic diseases and effectiveness of vitamin D supplementation to improve the clinical condition of the diseases will surely encourage the clinicians not to underestimate vitamin D deficiency as well as to include vitamin D supplements as a part of their therapeutic regime.

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