OPEN ACCESS at journalijcir.com

Research Article

ISSN: 2395 -5775

VITAMIN D DEFICIENCY - A RISK FACTOR FOR AUTO IMMUNE THYROIDITIS

C Jayakumari., B. Jayakumar., P.K. Jabbar., Abilash Nair*., SabooraBeegum M and Raina T Pillai

Abstract

Background: Vitamin D deficiency is being increasingly recognized globally as a significant health problem.There is an increasing prevalence of thyroiditis in India. Vitamin D Deficiency has been implicated in many autoimmune diseases. Literature is conflicting on the association between serum 25-Hydroxy vitamin D (25-OH-D) level and auto immune thyroiditis. This study was designed to find if there is an association between serum Vitamin D level and autoimmune thyroiditis.

*Methodology:*The study was conducted in the Department of Endocrinology, Govt. Medical College, Thiruvananthapuram, Kerala, India. Seventy five cases with autoimmune thyroiditis were compared to 75 age and sex matched healthy subjects with respect to serum 25-OH-Dlevel.

Results: Vitamin D levels were significantly low in cases than in controls(16.4 ±7.8ng/ml vs 29.4± 9.0ng/ml; p< 0.001). Serum25-OH-D levels < 20 ng/ml was more common in patients with autoimmune thyroiditis than controls with an odds ratio of 17.9 (95% CI 7.9-40.7).

Conclusion: Vitamin D deficiency has a significant association with autoimmune thyroiditis. Further research is needed to find causality of this association and to check whether vitamin D replacement can prevent or delay autoimmune thyroiditis.

Key Words: Autoimmune thyroid disease, Hypothyroidism, Vitamin D, Hashimotos thyroiditis

INTRODUCTION

Vitamin D is a fat soluble steroid pro-hormone produced endogenously in the skin by exposure to sunlight (1,2). Its major recognized role is in bone and calcium metabolism with a predominantly calcium conserving effect. Vitamin D deficiency is increasingly being seen globally as a major health problem (3). In recent years many reports have suggested that serum Vitamin D levels are low even in people living in tropical countries where exposure to sunlight is considered adequate (4,5). Majority of population in India lives in areas receiving ample sunlight throughout the year, still Vitamin D deficiency is common in all age groups and in both sexes across the country (6). The role of vitamin D deficiency in bone health is already well established (7). Auto immune thyroid disease is the most common organ specific autoimmune disease. Thyroiditis is defined as an organ specific autoimmune disorder characterized by diffuse goitre with lymphocytic infiltration and presence of thyroid specific autoantibodies (8). Autoimmune thyroid diseaseis predominantly a disease of cell mediated. The pathogenesis of autoimmune thyroid disease is multi factorial combining genetic, immune, environmental and hormonal influences which may include those by Vitamin D and its active forms (9,10).

A role forVitaminD has been proposed in cell growth, differentiation, apoptosis and an anti-carcinogenesis (11,12,13). Among the other extraskeletal actions of VitaminD, its role as an immune-modulator has been emphasized in recent years (9). The discovery of the Vitamin D receptors (VDR) in the monocytes, dendritic cells and activated T cells has highlighted the potential involvement of vitamin D in the pathogenesis of auto immune diseases (11). Specifically, VitaminD deficiency has been found to be associated with type 1 diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and Chron's disease (13). In the past several years it has been recognized that vitamin D deficiency may play a role in the etio-pathogenesis of auto immune thyroiditis. Similarly, in the recent years there is an increase in the incidence of auto immune thyroiditis (9, 15). At present, reports on the association of Vitamin D and auto immune thyroiditis are conflicting. This study was done to find out the association of Vitamin D deficiency with auto immune thyroiditis.

METHODOLOGY

The study was conducted in the Department of Endocrinology, Government Medical College Hospital Trivandrum which is a tertiary care teaching hospital. The study was conducted in a case control design and done over 6 months. The cases were patients diagnosed with autoimmune thyroiditis.

Department of Endocrinology and Metabolism and Department of Biochemistry, Government Medical College, Thiruvananthapuram, Kerala, India

Correspondence and Reprint Requests: Abilash Nair

Received: May,10 2017 | **Accepted:** June,15 2017 | **Published Online:** July,28 2017

Conflict of interest: None declared | **Source of funding:** Nil

Controls were healthy individuals with no family history of thyroid diseases. Ethical clearance for the study was obtained from Institutional Ethics committee. The research protocol was explained to all participants and written consent was obtained from all subjects. For this study, patients with a positive anti thyroid peroxidase antibody and a Fine Needle Aspiration Cytology (FNAC) report showing lymphocytic aspirate

were considered to have autoimmune thyroiditis. Patients having the above investigations done beforehand were included in to the study after considering exclusion criteria. Specifically, patients with confounding problems which are associated with vitamin D deficiency were excluded (Figure 1). All consecutive cases satisfying the criteria for thyroiditis attending the Endocrinology out-patient clinic during the study period were selected for the study. A total of 75 cases were assessed for vitamin D status. The demographic details and clinical assessment of thyroid function were noted on a predesigned proforma. The 25-OH-D levels were assessed by electro-chemiluminiscence(Elecsys 2010) using a commercial kit (Roche diagnostics, Germany). The intra-assay coefficient of variation of the method was <8 %. The current thyroid function was assessed using serum Thyroid Stimulating Hormone (TSH) (electro-chemiluminiscence, Elecsys 2010, Roche Diagnostics Germany test kits). Based on Endocrine Society Clinical Practice Guidlines we defined Vitamin D deficiency as 25-OH-Dlevel below 20 ng/ml, Vitamin D insufficiency as a level of 25-OH-D of20-30 ng/ml and sufficiency a level more than 30ng/ml. Patients with vitamin D levels less than 10 ng /ml were classified as severe deficiency.

For comparison seventy-five age and sex matched controls were assessed for 25-OH-Dlevels and current thyroid function status using the same assays as that of the cases. Data was analysed using Microsoft Excel and SPSS Version 20. Mean and Standard deviation were used for description of continuous variables and percentages for categorical variables. Continuous variables were compared using student t-test. Chi square test and Fischer's exact test were used for categorical variables as appropriate. As TSH levels exceeded or were lower than the detection limit in some patients it was expressed as median ± interquartile range and was compared using Mann-Whitney test.Strength of association was described using odds ratio where appropriate anda p-value of less than 0.05 was considered as statistically significant. Multivariate analysis was done using binary logistic regression.

RESULTS

Flow of patients and controls in the study is shown in Figure 1. The demographic and clinical characteristics of the cases and controls are compared in Table 1. Vitamin D status among cases and controls is compared in Table 2. Seventy- five cases with autoimmune thyroiditis were compared with seventy five healthy age and sex matched controls. The mean age of the cases was 32.37 ± 10.9 years whereas the mean age of the controls was 32.35 ± 9.0 years (p value- 0.98). Seventy three cases and 73 controls were females. Thus the controls were adequately age and sex matched(p >0.05). Further, there were no differences between the two groups regarding religion, socioeconomic status, marital status, non-vegetarianism, and body mass index.

All controls were euthyroid clinically and biochemically (median TSH was 1.74µlU/ml with an inter-quartile range of 1.14 to 3.20 µlU/ml). On analyzing the thyroid function status within the cases, it was found that 82.7 % of the cases were poorly controlled and 10.7 % of the cases were being over-treated. The mean vitamin D level among the controls was 29.4± 9.0ng/ml whereas that for the cases was 16.4 ±7.8ng/ml(p< 0.001). Vitamin D deficiency (25-OH-D<20 ng/ml was found in 58 cases (77.3%) whereas only 12 controls (16%) were vitamin D deficient and this difference was statistically significant (p<0.001). The odds ratio for this association was 17.9 (95% CI 7.9-40.7). Further on binary logistic regression Vitamin D level was found to be associated with autoimmune thyroiditis (adjusted odds ratio 22.3 ,95% CI 8.4-59.6) implying that Vitamin D deficiency is an independent association of autoimmune thyroiditis.

Fourteen cases with autoimmune thyroiditis had 25-OH-D level less than 10ng/mlwhereas none of the controls had a vitamin D level less than 10.(P<0.001). Within the cases 12 poorly controlled ones were having a 25-OH-Dlevel of 9 ng/ml or less whereas none of the rest 13 patients (euthyroid or over-treated) had such low levels although this association did not reach statistical significance (p value= 0.11).

DISCUSSION

Autoimmune disorders are more common in females (15,16) and as expected, in the present study majority of the cases were females. Most of the patients were under 25 years of age. Previous studies also show that autoimmune thyroiditis is common in adolescents and young adults (15). Autoimmune thyroiditis is the commonest cause of hypothyroidism in females of the reproductive age group. Hypothyroidism in pregnancy is associated with adverse maternal and fetal outcome (17,18). Hypo-thyroid patients are at high risk of obstetric complications even if diagnosed prior to pregnancy and started on thyroid replacement (19).

So identification of risk factors for autoimmune thyroiditis and its prevention is important to reduce the prevalence of hypothyroidism and its complications. The present study found that 82 % of the cases were poorly controlled and 10.7 % of the cases were being over-treated. This suggests that hypothyroidism treatment is far from adequate even in those receiving treatment.

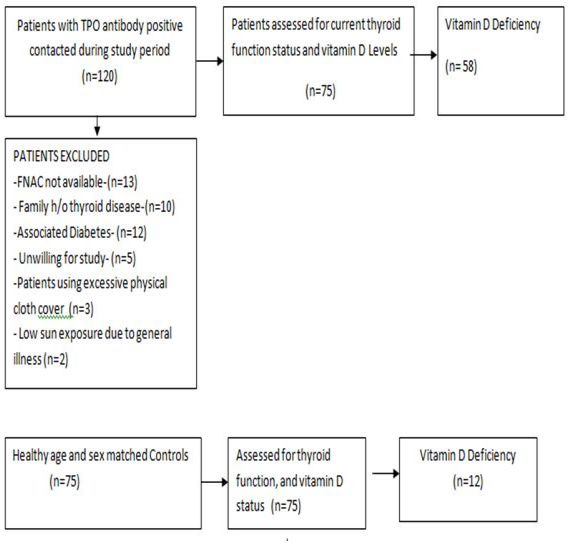

Figure -1 Flow of patients in study

Table-1 Comparison of demographic, clinical and biochemical variables between cases and controls

Parameter	cases	control	p-value
Mean Age (±SD) years	32.37 (10.9)	32.35 (9.0)	0.98
Sex, Females (%)	73 (97.3)	73(97.3)	1
Religion			
Hindu,n (%)	50 (66.7)	51 (68.0)	0.77
Christian, n(%)	17 (22.7)	14 (18.7)	
Muslim, n(%)	8 (10.6)	10 (13.3)	
Socio Economic status, Below poverty line (%)	27 (36.0)	21 (28.0)	0.29
Marital status, Married (%)	53 (70.7)	62 (82.7)	0.08
Diet, Non Vegetarian (%)	72 (96)	70 (93.3)	0.46
BMI kg/m^2(±SD)	25.5(4.7)	25.53 (3.4)	0.97
Clinical Status			
Adequately Controlled hypothyroidism, n (%)	5 (6.7)	75 (100.0)	<0.001
Inadequately controlled Hypothyroidism, n (%)	62 (82.7)	0 (0.0)	
Over-treated,n (%)	8 (10.7)	0 (0.0)	
TSH- median (inter-quartile range)	27.30 (10.8-50.0)	1.74 (1.14-3.20)	<0.001
Vitamin D level in ng/ml(±SD)	16.4 (7.8)	29.4 (9.1)	<0.001
Vitamin D < 10 ng/ml (%)	14 (18.7)	0 (0.0)	<0.01

Table- 2 Vitamin D deficiency and Autoimmune Thyroiditis

		Case		Control		p	OR
		N	%	N	%		
Vit. D Level	<20	58	77.3	12	16.0	<0.001	17.91 (CI 17.9-0.7)
	≥20	17	22.7	63	84.0		

This may also be a reflection of the referral bias as the cases were recruited from a tertiary care center where poorly controlled or over-treated patients were referred from peripheral hospitals.

The key observation from the present study is that Vitamin D deficiency is far more common in patients with auto immune thyroiditis when compared to age and sex matched healthy controls. Serum 25-OH-Dlevels less than 10 ng/ml (severe vitamin D deficiency) was found in 18.7% of the cases while none of the controls had such a finding suggesting that the prevalence of severe vitamin D deficiency was significantly higher in patients with autoimmune thyroiditis. It is also inferred that this association is independent of other variables such as TSH, age etc. Some previous studies have also revealed low 25-OH-Dlevel in patients with autoimmune thyroiditis (20, 21,22,23). The study by Kivity *et al* (9) revealed that the prevalence of Vitamin D deficiency is significantly higher in patients with autoimmune thyroiditis when compared to healthy controls similarly Bozkurt *et al* (2013) demonstrated that serum 25-OH-Dlevel of autoimmune thyroiditis patients were significantly lower than controls and the severity of deficiency was correlated with duration of autoimmune thyroiditis, thyroid volume and antibody levels (21). The two studies reported from India were from the northern (22) and eastern (23) part of the country. One study demonstrated a weak association of vitamin D deficiency with Autoimmune thyroid disease (AITD) (22), whereas the other has shown a significantly low level of 25-OH-D levels in AITD patients than in controls like in the observation made in the present study (23). In the present study it is further found that a significant number of the patients with autoimmune thyroiditis had poor control of hypothyroidism. Also, the number of persons with very low vitamin D levels was much higher in poorly controlled hypothyroid patients with a trend towards significance. This may suggest that vitamin D deficiency is an impediment to the adequate control of hypothyroidism. This is a novel observation and should stimulate further research to confirm the finding in larger population as well as to explore the reasons for such a phenomenon.

CONCLUSION

The results of our study show that Vitamin D deficiency is an association of auto immune thyroiditis. The risk is more with the severity of Vitamin D deficiency. Hence it may be prudent to screen people at high risk for thyroiditis - especially females of the reproductive age group for vitamin D deficiency and if found to be deficient, to give appropriate supplementation. Further studies are required to find out whether Vitamin D supplementation helps in control of auto immune thyroid diseases and thereby reduces the prevalence of autoimmune thyroid disease or not.

References

1. Deluca HF Evolution of our understanding of vitamin D. *Nutr, Rev*. 2008; 66 (10) 73-87.
2. Hollick M F, Vitamin D: The underappreciated D lightful hormone that is important for skeletal and cellular health. *Curr.opin Endocrinol Diabetes* 2002. 9(1) 87-98.

3. Hollick M F, Chen T .C, Vitamin D deficiency a worldwide problem with health consequences. *Am. J. Clin Nutr* 2008; 87
4. Oren Y. Shapira Y, Agmen Levin, *et al* Vitamin D insufficiency in a sunny environment a demographic and seasonal analysis Isssr Med Assoc l 2010;12;751-756.
5. Goswami R, Gupta N, Goswami D, Marwaha RK, Tandon N, Kochupillai N. Prevalence and significance of low 25-hydroxyvitamin D concentrations in healthy subjects in Delhi. *Am J Clin Nutr* (2000) 72(2):472-5
6. Ritu G, Gupta A. Vitamin D deficiency in India: Prevalence, Causalities and Interventions. *Nutrients* 2014, 6, 729-775.
7. ArnsonY, Amital H, Shoenfeld Y Vitamin D and autoimmunity: new aetiological and therapeutic considerations. *Ann Rheum Dis* 2007 66:1137-1142.
8. Hiromatsu Y, Satoh H, Amino N: Hashimotos Thyroiditis: History and Future Outlook - Review. *Hormones* 2013,12(1); 12-18..
9. Kivity S,Agmon N, Levin,Zisappl M. ShapiraY, Nagy EV, Dankó K, Szekanecz Z, Langevitz P and Shoenfeld Y. Vitamin D and autoimmune thyroid diseases. *Cellular and molecular Immunology* 2011. 243-247
10. Hollick M.F, BinkelyN.CBischoff, Ferrari HA, Evaluation, treatment and prevention of Vitamin D deficiency : an Endocrine Society Clinical Practice Guideline. *J ClinEndocrinol. Metab* 2011: 96: 1911-30
11. BaekeF, Takiishi.T, Korf.H, Gysemans.C Vitamin D-Modulator of the immune system. *CarrOpinRhermecol*2010 10:482-496
12. Cantorna MT, Mahoon B.D. Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. *ExpBiol Med (Maywood)* 2004. 229:1136-1142
13. Kivity, Agmon – Levin N, Zisappl M *et al* Vitamin D and autoimmune thyroid disease Cell Mol Immunol.2011;8:243-7.
14. Hollick M Vitamin D Photobiology, Metabolism, Mechanism of action and clinical application. 5thed: Washington DC 2003.
15. UshaMenon V, Sundaram KR, Unnikrishnan AG, Jayakumar RV, Nair V Kumar. High prevalence of undetected Thyroid disorders in an Iodine sufficient adult south Indian population. *J Indian Med Assoc* 2009 Feb; 107(2) 72-7.
16. Pearce EN, Farwell AP, Braverman L E Thyroiditis. NEJM 2003 348:2646-2655.
17. Sahay RK and Nagesh VS. Hypothyroidism in pregnancy. *Indian J EndocrinolMetab*. 2012 May-Jun; 16(3): 364-370.
18. Barbel P Mestre JL, SantanmariaA, PalazonI, Franco A, Graelis M, *ét al*. Delayed neurobehavioral development in children born to pregnant women with mild hypothyorixinemia during the first month of gestation; the importance of early iodine supplementation. *Thyroid* 2009 may: 19(5):511-9.
19. Nirmala C, Jayakumari C, RajasekharanC, Nandini V.R., Maternal outcome of hypothyroidism in pregnancy - A South Indian Perspect. *American journal of clinical medicine research.* 2004 vol2, No. 2, 47-50.
20. LackaK, Macicjewski A, Vitamin D in the etiopathogenesis of autoimmune thyroidities. *Pal MerkurLekarski* 2013;34:281-5.
21. Bozkurt NC, Karbek B, Ucan B *et al*. The association between severity of Vitamin D deficiency Hashimotos thyroiditis. *Endocr.Pract.*2013;19:479-84.
22. Goswami R, Marwaha RK, Gupta N, Tandon N, Sreenivas V, Tomar N, Ray D, Kanwar R, AgarwalR. Prevalence of vitamin D deficiency and its relationship with thyroid autoimmunity in Asian Indians: a community-based survey. *Br J Nutr.* 2009 Aug;102(3):382-6.
23. Halder T, Bhattacharya S. Prevalence of Hashimotos Thyroiditis and its association with Vitamin D Deficiency in West Bengal, India *British Journal of Medicine & Medical Research* 12(7): 1-10, 2016.

****