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Original Research Article

Vitamin D status in children with autoimmune thyroiditis

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ABSTRACT

Background: Deficiency of 25 hydroxyvitamin D has been linked with predisposition to autoimmune disorders. Also, vitamin D has been found to be a causal factor in many autoimmune diseases. Objective of the study was to investigate vitamin D status in children with autoimmune thyroiditis attending endocrinology OPD at a tertiary centre in southern India.
Methods: It is a case control study done in which 75 children (70 female, 5 male) with age and sex matched healthy controls were chosen. Free thyroxine, TSH, anti TPOAb, anti TGAb, 25 hydroxyvitamin D, serum calcium, phosphorus, alkaline phosphatase levels were estimated in both cases and control subjects. Children with anti TPO or anti TG positivity were divided into four groups based on their level of antibody titers.
Results: The mean age in cases was 9.8±0.34 years. 25(OH)D levels were significantly lower in cases (15.07±1.14 ng/ml) compared to controls (17.82±1.13 ng/ml) ($p<0.0006$). Mean serum calcium levels in cases (9.35±0.16 mg/dl) were significantly lower when compared to controls (9.73±0.14 mg/dl) ($p<0.0005$). Similarly, mean serum alkaline phosphatase level in cases (184.97±11.10 IU/L) were significantly elevated when compared with controls (122.37±6.82 IU/L) ($p<0.0001$). However, there was no significant difference in serum phosphorus levels between cases (4.42±0.10 mg/dl) and controls (4.43±0.14 mg/dl) ($p=0.83$). There was no significant difference in vitamin D level among the groups in both anti TPO ($p< 0.283$) and anti TG ($p<0.148$).
Conclusions: The significant decrease in vitamin D levels in cases signifies that 25(OH)D may be an independent causal factor related to the autoimmunity in thyroid diseases.

Keywords: Autoimmune thyroiditis, Vitamin D

INTRODUCTION

Autoimmune Thyroiditis is the most common cause of thyroid disease in children and adolescents. It is also the most common acquired cause of hypothyroidism with or without goiter. Autoimmune thyroid disease is evident in 6% of children aged 12-16yrs with female: male preponderance of 2:1. Autoimmunity may be attributed to environmental triggers and susceptible genes which are involved in immunoregulation. T cells are the predominant infiltrating lymphoid cells which constitutes around 60%, B cells constitutes around 30%. Cytotoxic (CD8) cells mediate thyroid gland destruction, there is production of cytokines like TNF, IL-1 and IFN-gamma which renders thyroid cells susceptible to apoptosis and impairment of thyroid function.

Vitamin D has pleiotropic immunomodulatory effects on innate and adaptive immune cells.[1-4] Vitamin D binds to the intracellular vitamin D receptor (VDR) which is present in many immune cells.[1] Apart from expressing VDR, immune cells (antigen presenting cells, T cells) also express enzymes needed for vitamin D metabolism to its active form.[1] Autoimmune thyroid diseases (AITD) occur due to imbalance of T helper 1 cells (Th1) and T helper 2 (Th2) cells. Patients with autoimmune thyroiditis

have increased production of Th1 cells which secretes IFN-gamma.[5] Cytokines secreted from Th17 cells are also involved in development of AITD. IFN-gamma and Interferon 17A mRNA is also highly expressed in autoimmune thyroiditis. Vitamin D plays an important role in regulating Th1, Th2 and Th17 cells and secretion of IFN-gamma, IL-17 and IL4.[6,7] This explains why thyroid autoimmunity is associated with lower levels of vitamin D.[5] Low level of vitamin D is found in association with excessive production of TRAb (Grave's disease), anti TPOAb and anti TGAb.[8]

METHODS

This study was conducted between August 2015 and September 2016 at Institute of Child Health and Hospital for Children, Chennai which is a tertiary care centre for Pediatrics with referrals from across the state including neighboring states. It is a Cross Sectional Case Control study done in children attending endocrinology OPD of Institute of Child and Hospital for Children. All newly diagnosed patients (6 to 12 yrs) presenting with goiter and/or hypothyroidism who on evaluation found to have autoimmune thyroiditis as evidenced by positive Anti Thyroid peroxidase antibodies and/or positive Anti Thyroglobulin antibodies were included as cases. Age and sex matched healthy children attending School health cell were taken as controls. Patients with proven vitamin D deficiency or on drugs like vitamin D, Calcium, Steroids, anti-epileptics were excluded from the study. Sample size of 75 cases and 75 controls calculated assuming a power of 80%, alpha error of 0.05 using pooled variation from previous study in children.[9]

25 hydroxyvitamin D, S. Calcium, S. Phosphorus, S. Alkaline phosphatase level, free Thyroxine and TSH level, anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies were measured in both cases and controls. Free thyroxine and TSH levels were measured using enzyme immunoassay method. Autoimmune antibody levels namely, anti-thyroid peroxidase antibodies and thyroglobulin antibodies were measured using chemiluminescence assay. Positive titers of antibody were considered significant.

25 hydroxyvitamin D levels were measured using chemiluminescence assay. X ray bone age was done in cases to assess skeletal maturation.

Descriptive statistical analysis was done using Gnumeric spreadsheet 1.12.28. Inferential statistics was done using R version 3.2.3 (2015-12-10) "Wooden Christmas-Tree" with basic statistical packages (Platform: X86_64_linux_gnu (64-bit)). Comparison of vitamin D level between groups was done using Student's t test since collected data followed normal distribution. Children with Anti-thyroid peroxidase antibody and Antithyroglobulin antibody were subdivided into four groups based on their serum concentration (less than 10, 10-100, 100-1000 and more than or equal to 1000). ANOVA for Vitamin D level was done among four groups in each class of antithyroid antibodies.

RESULTS

The most common age group in our study was between 10-12 yrs. 49 (65%) children belonged to this age group. Age distribution in cases is skewed to the left which may be due to very few numbers of autoimmune thyroiditis occurring in younger age group. Female children were most commonly affected with autoimmune thyroiditis. Among 75 children, 70 (93%) children were female and 5 (7%) were male. The female: male ratio was 14:1. Goitre (92%), lassitude (33%) and constipation (21%) were the most common presenting symptoms. In autoimmune thyroiditis group, 10 (13.3%) children were euthyroid, 13 (17.3%) children had subclinical hypothyroidism and 52 (69.3%) had overt hypothyroidism.

ANOVA (Analysis of Variance) analysis of 25 hydroxyvitamin D level was done between the four groups of children with anti-thyroid peroxidase antibody. It was found that there was no statistically significant difference among these four groups (p=0.283). F statistics =1.29.

Table 1: Distribution of cases with mean vitamin D level across various levels of anti-thyroid peroxidase antibodies.

Anti TPO groups	Count (no. of cases)	Average 25 OH vitamin D (ng/ml)
<10	10	15.1
10-100	22	14.7
100-1000	24	14
≥1000	19	16.9

ANOVA (Analysis of Variance) analysis of vitamin D level was done between the four groups of children with anti-thyroglobulin antibody. It was found that there was no statistically significant difference among these four groups (p=0.148). F statistics=1.84.

Table 2: Distribution of cases with mean vitamin D level across various levels of antithyroglobulin antibodies.

Anti TG groups	Count (no. of cases)	Average 25 OH vitamin D (ng/ml)
<10	8	12.1
10-100	29	15.7
100-1000	31	14.7
≥1000	7	17.6

25(OH)D levels were significantly lower in cases (15.07±1.14 ng/ml) compared to controls (17.82±1.13 ng/ml) (p<0.0006). Mean serum calcium levels in cases (9.35±0.16 mg/dl) were lower when compared to controls (9.73±0.14 mg/dl). This difference is statistically significant (p<0.0005). Similarly mean alkaline

phosphatase level in cases (184.97±11.10 IU/L) was significantly elevated when compared with controls (122.37±6.82 IU/L) (p<0.0001). However, there was no significant difference in serum phosphorus levels between cases (4.42±0.10 mg/dl) and controls (4.43±0.14 mg/dl) (p=0.83).

Table 3: Summary of biochemical parameters in cases and controls.

	Hashimoto group (n=75)	Control group (n=75)	p value
25(OH)D, ng/ml	15.07±1.14	17.82±1.06	0.0006
Calcium, mg/dl	9.35±0.16	9.73±0.14	<0.0005
Phosphorus, mg/dl	4.42±0.10	4.43±0.14	0.83
Alkaline phosphatase, IU/L	184.97±11.10	122.37±6.82	<0.0001

X ray bone was done in all patients to look for any delay or advancement in bone age. Bone age was advanced in most of the cases. This may be explained because female children between 10-12 yrs of age were mostly commonly affected and advancement may be due to the pubertal progression in these female children.

DISCUSSION

VDR has been found to be present in wide range of cells including B cells, T cells, monocytes and macrophages. Deficiency of 25 hydroxyvitamin D has been linked with predisposition to autoimmune disorders. Also, vitamin D has been found to be a causal factor in many autoimmune diseases.[10] This relationship is being investigated to study the role of this hormone in immune regulation. There have been many studies done outside India to find the association between vitamin D deficiency and autoimmune thyroiditis. This is the first study done in Indian children to investigate vitamin D status in children with autoimmune thyroiditis. In our study 75 children with autoimmune thyroiditis were included as cases and 75 age and sex matched children as healthy controls. Among 75 children, 70 (93%) were female and 5 (7%) were male which indicates the high prevalence of autoimmune thyroiditis in female sex. The most common age group in our study subjects was between 10-12 yrs (65%). Goiter (92%), lassitude (33%) and constipation (21%) were the most common presenting symptoms.

49 (65%) children with Hashimoto thyroiditis were between 10 to 12yrs of age. In autoimmune thyroiditis group, 10 (13.3%) children were euthyroid, 13 (17.3%) children had subclinical hypothyroidism and 52 (69.3%) had overt hypothyroidism. There was no significant difference in vitamin D levels among these groups. Also, there was no statistical significant difference in vitamin D levels among the groups in both anti TPO (p <0.283) and anti TG (p <0.148). This finding is consistent with the Ravinder Goswami et al study done in Indian adults which also showed only weak inverse correlation between serum 25(OH) D and TPOAb titres.[4] But this finding is contradictory to the study done by Dong Yeob Shin et al, Shane Kivity et al and Carmurdan et al.[11,12,9]

25(OH)D levels were significantly lower in cases (15.07±1.14 ng/ml) compared to controls (17.82±1.13 ng/ml) (p <0.0006). This finding is similar to the study done by Carmurdan et al, Dong Yeob Shin et al, Shane Kivity et al,Tamer G and Esmat Fawzy et al study.[9-13] Though there was no significant difference in vitamin D levels between the euthyroid, overtly hypothyroid or subclinical hypothyroid groups.

Mean serum calcium levels in cases (9.35±0.16 mg/dl) were lower when compared to controls (9.73±0.14 mg/dl). This difference is statistically significant (p <0.0005). Similarly mean alkaline phosphatase level in cases (184.97±11.10 IU/L) was significantly elevated when compared with controls (122.37±6.82 IU/L) (p <0.0001). However, there was no significant difference in serum phosphorus levels between cases (4.42±0.10 mg/dl) and controls (4.43±0.14 mg/dl) (p=0.83).

The significant difference in calcium and alkaline phosphatase levels between cases and controls is consistent with Carmurdan et al study done in children but is in contrast to the study done in adults by Dong Yeob Shin et al in which there was no significant difference in calcium levels between AITDs and non-AITDs group.[9,11] The absence of significant difference in phosphorus levels between cases and control groups is contrast to the study done by Carmurdan et al.[9] This signifies that in vitamin D deficiency, absorption of dietary calcium and phosphorus is decreased. But majority of serum phosphorus levels is contributed by dietary phosphorus, absorption of which is independent of vitamin D.[14] This may explain the absence of significant difference in serum phosphorus levels between cases and controls.

CONCLUSION

Children with autoimmune thyroiditis have low vitamin D levels though there is no negative correlation between anti TPO antibody and vitamin D levels.

The significant decrease in vitamin D levels in cases signifies that 25(OH)D3 may be an independent causal factor related to the autoimmunity in thyroid diseases. Future studies should focus in vitamin D usage as an agent to prevent, postpone or reduce the symptoms related to Hashimoto thyroiditis.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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