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Prevalence of vitamin D deficiency and its relationship with thyroid autoimmunity in Asian Indians: a community-based survey

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25-Hydroxy vitamin D (25(OH)D) deficiency is linked with predisposition to autoimmune type 1 diabetes and multiple sclerosis. Our objective was to assess the relationship between serum 25(OH)D levels and thyroid autoimmunity. Subjects included students, teachers and staff aged 16–60 years (total 642, 244 males, 398 females). Serum free thyroxine, thyroid-stimulating hormone (TSH), and thyroid peroxidase autoantibodies (TPOAb), intact parathyroid hormone and 25(OH)D were measured by electrochemiluminescence and RIA, respectively. Thyroid dysfunction was defined if (1) serum TSH $\geq$ 5 μU/ml and TPOAb $>$ 34 IU/ml or (2) TSH $\geq$ 10 μU/ml but normal TPOAb. The mean serum 25(OH)D of the study subjects was 17·5 (SD 10·2) nmol/l with 87 % having values $\leq$25 nmol/l. TPOAb positivity was observed in 21 % of subjects. The relationship between 25(OH)D and TPOAb was assessed with and without controlling for age and showed significant inverse correlation (r −0·08, P=0·04) when adjusted for age. The prevalence of TPOAb and thyroid dysfunction were comparable between subjects stratified according to serum 25(OH)D into two groups either at cut-off of $\leq$25 or $>$25 nmol/l or first and second tertiles. Serum 25(OH)D values show only weak inverse correlation with TPOAb titres. The presence of such weak association and narrow range of serum 25(OH)D did not allow us to interpret the present results in terms of quantitative cut-off values of serum 25(OH)D. Further studies in vitamin D-sufficient populations with wider range of serum 25(OH)D levels are required to substantiate the findings of the current study.

25-Hydroxy vitamin D: Vitamin D deficiency: Thyroid autoimmunity

Until recently, vitamin D deficiency was considered to be rare in India because of abundant sunshine[1,2]. However, a systematic study carried out in the year 2000 in Delhi showed the presence of low 25-hydroxy vitamin D (25(OH)D) in a majority of subjects including newborns, their mothers, healthy physicians, nurses, soldiers and those with vitiligo and albinism. Based on these study groups, subnormal serum 25(OH)D levels of Asian Indians could be linked to their skin pigmentation and poor sunshine exposure[1,3]. Subsequently, a series of studies have documented widespread hypovitaminosis D in north as well as south India[3–5].

Besides bone mineral homeostasis, 25(OH)D deficiency has been associated with a wide range of non-skeletal effects including predisposition towards autoimmune disorders[6–8]. The demonstration of vitamin D receptor in monocytes, dendritic cells and activated T cells indicates significant interaction between vitamin D and the immune system[6,7]. While the molecular mechanisms linking vitamin D with autoimmunity are under investigation, *in vitro* studies indicate an immunomodulatory effect of 1,25(OH)D on Th_1, Th_2, T regulator and dendritic cells leading to a shift towards activation of Th2 cells[6,7]. Clinical relevance of the mechanism is indicated by a number of studies showing increased prevalence of autoimmune disease such as multiple sclerosis in Canada and the northern part of the USA receiving less sunshine. Vitamin D supplementation resulted in decreased prevalence of autoimmune disorders such as type 1 diabetes and multiple sclerosis. A recent meta-analysis showed 29 % reduction in the risk of type 1 diabetes in children receiving vitamin D supplementation[9,10]. Similarly, in multiple sclerosis every 50 nmol/l increase in serum 25(OH)D levels in a healthy Caucasian population reduced the risk of disease by 41 %[11].

Recent studies using thyroid microsomal or thyroid peroxidase autoantibodies (TPOAb) have revealed a high prevalence of thyroid autoimmunity in the general population in India[12,13]. Autoimmune hypothyroidism has been estimated to be the most frequent endocrine autoimmune disorder and

Abbreviations: iPTH, intact parathyroid hormone; 25(OH)D, 25-hydroxy vitamin D; PTH, parathyroid hormone; TPOAb, thyroid peroxidase autoantibodies; TSH, thyroid-stimulating hormone.

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possibly affects approximately 42 million people in India[14]. Currently, the prevalence of thyroid autoimmunity in children is as high as 9–13 %[12]. To the best of our knowledge, there is no study which has assessed the relationship between 25(OH)D deficiency and thyroid autoimmunity. The current study has been carried out to assess the relationship, if any, between thyroid autoimmunity and serum 25(OH)D levels in Asian Indians.

Material and methods

The study was carried out in four schools and a medical college of Delhi in November 2006 to March 2007, corresponding to winter months in India. These educational institutions were selected based on convenience including availability of consent from the authorities to carry out the studies among students, teachers and non-teaching staff, and their proximity to the institutions of the participating investigators. Consent was also obtained from study participants and parents of school children. The school and colleges selected were fee-paying and most of the study subjects belonged to the middle-income group. A day prior to the survey, school visits were made and subjects were instructed to report fasting the next day. Subjects <16 years of age, or on drugs affecting bone mineral metabolism such as calcium, vitamin D, glucocorticoids, antitubercular and antiepileptics were excluded from the present study. A total of 642 subjects were recruited ((244 males and 398 females; mean age 33·7 (SD 13·5) years (range 15–60 years)). Fasting blood samples were drawn for the estimation of serum 25(OH)D, intact parathyroid hormone (iPTH), total calcium, inorganic phosphorus, alkaline phosphatase, serum free thyroxine, thyroid-stimulating hormone (TSH) and TPOAb. Blood was transported in chilled containers to the All India Institute of Medical Sciences for hormone and TPOAb estimation.

Assays

Biochemical estimations were carried out using an automated analyser (Hitachi 902; Roche, Mannheim, Germany) and commercial kits (Roche). The normal range for serum total calcium, inorganic phosphorus, alkaline phosphatase and total magnesium were 2·0–2·6 mmol/l, 0·8–1·45 mmol/l, 98–279 IU/l and 0·65–0·90 mmol/l, respectively. Intra-assay and inter-assay CV for these assays ranged between 3·5 and 5·0 %. Serum 25(OH)D was measured using RIA (Diasorin, Stillwater, MN, USA). Serum samples for the measurement of free thyroxine, TSH, TPOAb and iPTH were stored at −20°C and assayed together in multiple batches by an Elecsys immunoassay kit autoanalyser (Elecsys-2010; Roche). The normal ranges for serum free thyroxine, TSH, TPOAb and iPTH were 12–22 pmol/l, 0·27–4·2 μU/ml, >34·0 IU/ml and 1·6–6·9 pmol/l, respectively. Inter- and intra-assay CV for these measurements were 2·9, 8·6, 6·3 and 1·6 % and 6·6, 8·7, 9·5 and 3·9 %, respectively). The Institutional ethics committee approved the study protocol and written informed consent was obtained from all the study subjects. The consent for the study and the final recruitment varied between 85 and 90 % in the study subjects from different schools and the medical college.

Definitions

Hypovitaminosis D. For the purpose of the current study, significant hypovitaminosis D was defined as serum 25(OH)D levels ≤25·0 nmol/l. This value was based on scatterplot and linear regression analysis between serum 25(OH)D and iPTH as reported in our earlier study[15]. Scatterplot showed a steep and curvilinear relationship between parathyroid hormone (PTH) and 25(OH)D in the first (12·2 nmol/l) and second tertile (≤25·0 nmol/l). Linear regression analysis also showed a significant rise in PTH at the 25(OH)D level of 10–14 nmol/l[15].

Thyroid autoimmunity. TPOAb positivity and thyroid dysfunction were defined as described earlier[13,16]. These definitions were based on the isolated or composite criteria currently used to define thyroid autoimmunity and thyroid dysfunction by the American Association of Clinical Endocrinologists, the American Thyroid Association and the Endocrine Society[16,17].

Thyroid peroxidase autoantibody positivity. Serum TPOAb titres >34 IU/ml were considered positive (Roche). To assess high-titre TPOAb positivity, an arbitrary cut-off of 103 IU/ml (three times above the normal) was also used.

Thyroid dysfunction. Subjects were considered to have clinically relevant thyroid dysfunction if they had (1) serum TSH of at least 5 μU/ml along with TPOAb >34 IU/ml or (2) TSH of at least 10 μU/ml but normal TPOAb titres.

Statistical analysis

The data are given as means and standard deviations. Statistical analysis was performed with SPSS statistical software version 10.0 (SPSS Inc., Chicago, IL, USA). Student's t test and χ^2 test with Yates correction was used to assess the significance of differences in the quantitative and frequency data. $P<0·05$ was considered significant.

Results

Table 1 gives the baseline characteristics of study subjects including their mean age, BMI, serum total calcium, inorganic phosphorus, alkaline phosphatase, 25(OH)D, iPTH and TPOAb positivity as well as sex-related differences in these parameters.

Prevalence of 25-hydroxy vitamin D deficiency

The mean serum 25(OH)D value of study subjects was 17·5 (SD 10·2) nmol/l; 87 % (95 % CI 84·5, 89·6) of subjects had 25(OH)D ≤25 nmol/l. There was no significant difference in the frequency of hypovitaminosis D between males and females (85·2 and 88·2 %, respectively, $P=0·169$). Though females had significantly higher BMI, there was no significant correlation between serum 25(OH)D and BMI or body weight in the whole group (r 0·022 and 0·020, respectively, $P>0·5$ for both) as well as in females (r 0·063 and 0·049, respectively, $P>0·5$ for both).

The mean serum total magnesium value was normal and only three (0·5 %) individuals had serum total magnesium in the subnormal range. There was an inverse relationship between 25(OH)D and PTH (r −0·184, $P<0·001$).

Table 1. Characteristics of the study subjects and sex-specific differences

Parameters	All subjects		Males		Females		*P* value between males and females
	Mean	SD	Mean	SD	Mean	SD	
n	642		244		398		
Mean age (years)	33·7	13·5	31·4	13·4	35·1	13·4	<0·01
BMI (kg/m^2)	24·9	9·0	23·6	4·2	25·3	5·0	<0·01
Serum total calcium (mmol/l)	2·50	0·16	2·54	0·16	2·47	0·15	<0·01
Serum inorganic phosphorus (mmol/l)	1·19	0·20	1·21	0·21	1·18	0·19	0·12
Serum alkaline phosphatase (IU/l)	241	113	285	122	215	70	<0·01
Serum 25(OH)D (nmol/l)	17·5	10·2	18·0	9·1	17·2	10·9	0·31
iPTH (pmol/l)	6·10	3·27	6·03	2·84	6·15	3·51	0·65
TPOAb positivity (%)*	20·9		16·4		23·6		0·04

iPTH, intact parathyroid hormone; 25(OH)D, 25-hydroxy vitamin D; TPOAb, thyroid peroxidase autoantibodies.
* TPOAb titres >34·0 IU/ml.

The *r* value between these two parameters remained the same even after controlling for serum total magnesium on partial correlation analysis. Biochemical hyperparathyroidism, indicated by serum iPTH >6·9 pmol/l, was present in 28·5 % of subjects and its frequency was not significantly different between males and females (28·3 and 28·6 %, respectively, *P*=0·498). The frequency of biochemical hyperparathyroidism was significantly higher in those with serum level ≤25·0 nmol/l as compared to those with levels >25 nmol/l (31·1 and 10·8 %, respectively, *P*<0·001).

Prevalence of thyroid autoimmunity

TPOAb positivity was found in 21 % (95 % CI 17·7, 24·0) of subjects. Eighty-four (62·7 %) of the subjects had TPOAb titres >103 IU/ml. The frequency of TPOAb positivity (cut-off 34 IU/ml, 23·6 and 16·4 %, *P*=0·035) and those with TPOAb titres >103 IU/ml (15·6 and 9·0 %, *P*=0·01) were higher in females as compared to the males. Interestingly, there was a significant positive relationship between serum TPOAb titres and age in the present study population (*r* 0·170, *P*<0·001). Thyroid dysfunction was present in 100/642 (15·65 %) subjects. Eighty-four of these had TPOAb >34·0 IU and TSH >5 μU/ml (13·1 %, males 9·0 % and females 15·6 %, *P*=0·01) and 16 (2·5 %) had only TSH levels >10·0 μU/ml with no TPOAb positivity (males 1·6 % and females 3·0 %, *P*=0·20).

Inter-relationship between 25-hydroxy vitamin D deficiency and thyroid peroxidase autoantibody positivity

The correlation coefficient between TPOAb and 25(OH)D (*r* −0·044, *P*=0·268) and between serum TPOAb titres and PTH (*r* 0·064, *P*=0·107) were not significant. In view of the fact that serum TPOAb significantly correlated with age, the relationship between 25(OH)D and TPOAb was also assessed using partial correlation analysis after controlling for age. The results showed significant inverse correlation between the two parameters (*r* −0·08, *P*=0·04).

Serum 25-hydroxy vitamin D and its relation to parameters of thyroid autoimmunity. The prevalence of thyroid autoimmunity at cut-off of 34·0 and 103 IU/ml, the mean TPOAb titres and frequency of thyroid dysfunction between groups with serum 25(OH)D ≤25·0 and >25·0 nmol/l are shown in Table 2. Though, the two groups stratified on the basis of 25(OH)D cut-off had significantly different mean 25(OH)D and iPTH levels, none of the parameters related to prevalence of thyroid autoimmunity including frequency of thyroid dysfunction were significantly different in the two groups. The differences in the parameters related to thyroid autoimmunity

Table 2. Thyroid autoimmunity in relation to serum 25-hydroxy vitamin D (25(OH)D) levels*
(Mean values and standard deviations)

Parameters	25(OH)D levels ≤25·0 nmol/l (*n* 559)		25(OH)D levels >25·0 nmol/l (*n* 83)		OR	95 % CI	*P*
	Mean	SD	Mean	SD			
Serum PTH (pmol/l)	6·3	4·0	4·8	1·8			<0·001
Serum 25(OH)D (nmol/l)	14·5	3·5	37·5	16·3			<0·001
TPOAb (>34 IU) (%)	21·3		18·1		1·23	0·65, 2·33	0·56
Mean TPOAb titres (IU/ml)†	58·0	4·9	45·8	10·4			0·36
TPOAb titres >103 IU/ml (%)	13·2		12·0		1·1	0·53, 2·41	0·86
Thyroid dysfunction							
TPOAb >34 IU/ml and TSH >5 IU/ml (%)	13·2		12·0		1·1	0·53, 2·41	0·86
TSH >10 μU/ml and TPOAb <34 IU/ml (%)	2·5		2·4		1·04	0·22, 6·75	0·74

25(OH)D, 25-hydroxy vitamin D; PTH, parathyroid hormone; TPOAb, thyroid peroxidase autoantibodies; TSH, thyroid-stimulating hormone.
* For details of procedures and subjects, see the Material and methods section and Table 1.
† Data shown as means and standard errors of the mean because of high standard deviations of the data.

were also looked after the study subjects were stratified into tertiles according to their serum 25(OH)D levels. Although the mean serum 25(OH)D values between subjects in the first and third tertiles were significantly different (12·23 (SD 0·2) and 27·0 (SD 13·4) nmol/l), prevalence of TPOAb positivity either at a cut-off of 34·0 (22·3 % *v.* 19·0 %) or at 103 IU/ml (14·4 % *v.* 11·8 %) was comparable in these tertiles. Similarly, prevalence of thyroid dysfunction (TSH $>10{\cdot}0\,\mu$U/ml and TPOAb negative; 2·7 % *v.* 3·3 % and TSH $>5{\cdot}0$ but TPOAb positive; 14·4 % *v.* 11·8 %) was comparable between the subjects in the first and third tertiles.

Thyroid autoimmunity and its relation to 25-hydroxy vitamin D status. The mean serum 25(OH)D, iPTH and frequencyof subjects showing biochemical hyperparathyroidism (iPTH $>6{\cdot}9$ pmol/l) were not significantly different in serum TPOAb-positive and -negative individuals (17·4 (SD 12·3) and 17·5 (SD 9·6) nmol/l; 6·2 (SD 3·4) and 6·1 (SD 3·2) pmol/l; 28·4 and 28·5 %, respectively). Similarly all the above parameters were not significantly different between groups with TPOAb titres ≤ 103 or >103 IU/ml.

Discussion

The observation that the mean 25(OH)D levels were as low as 17·5 (SD 10·2) nmol/l and that 85 % of study participants had levels ≤ 25 nmol/l, confirms our earlier reports of wide prevalence of hypovitaminosis D in apparently healthy Asian Indians[1–5]. Though the present study was carried out in the winter months when the serum 25(OH)D values are expected to be low, one of our previous studies showed that the mean serum 25(OH)D values were far below the optimum level (17·9 (SD 7·9) nmol/l) in Asian Indians even during the summer months[1]. The findings of the current study showing hypovitaminosis D in a large number of Asian Indians assume further importance in view of the fact that deficiency was observed in subjects recruited from teaching institutions despite nearly a decade of awareness about the presence and the contributory factors of vitamin D deficiency in Delhi[1]. Recently, we have also observed the absence of any change in vitamin D receptor expression levels in subjects with hypovitaminosis D[10]. These facts indicate lack of bio-adaptation of vitamin D receptor levels in man and a need for continued efforts to highlight the wide prevalence of hypovitaminosis even in countries with an abundance of sunshine and a vitamin D fortification programme[18].

In our previous studies, we have documented the functional significance of vitamin D deficiency in Asian Indians in terms of its association with a rise in serum PTH levels[1,11], decreased bone mineral content[5] and poor dietary calcium absorption from the intestine. Recently, 25(OH)D deficiency has also been associated with a wide range of non-skeletal disorders including malignancies, coronary artery disease and autoimmune disorders such as type 1 diabetes and multiple sclerosis[9]. A recent meta-analysis showed a 29 % reduction in the risk of type 1 diabetes in children receiving vitamin D supplementation[12,13]. Similarly, in multiple sclerosis every 50 nmol/l increase in serum 25(OH)D levels in a healthy Caucasian population reduced the risk of disease by 41 %[14].

Though autoimmune thyroid disorders are more prevalent than type 1 diabetes and multiple sclerosis, there has been no study assessing association between thyroid autoimmunity and 25(OH)D status. The high prevalence of TPOAb and thyroid dysfunction observed in the current study involving a large cohort of the population is similar to that reported in healthy Indians of a similar age group[7]. The presence of TPOAb positivity in up to 21 % of the general population in India and thyroid dysfunction in up to 15 % of them could possibly be related to the successful salt iodisation programme which has been ongoing in India since 1992. Similar high prevalence of TPOAb and thyroid dysfunction has also been reported in a population-based survey from an iodine-sufficient region of Western Australia[16]. Walsh *et al.*, while studying the relationship of thyroid autoimmunity with parity observed 26 % prevalence of TPOAb positivity or TSH elevation in 1045 women from the general population[16].

The presence of a high prevalence of thyroid autoimmunity and vitamin D deficiency in the Indian population provided us with a unique opportunity to assess association between these two variables. The results of the current study indicate the presence of a significant inverse association between 25(OH)D levels and thyroid autoimmunity as reflected in TPOAb titres. Though the relationship assumed statistical significance, the R^2 value was only 0·006, indicating that only 0·6 % variation in thyroid autoimmunity was determined by 25(OH)D levels in the present study population. The presence of such a weak association and narrow range of serum 25(OH)D values did not allow us to interpret the present results in terms of quantitative cut-off values of serum 25(OH)D either in groups with serum 25(OH)D >25 nmol/l or in those with serum 25(OH)D values in the third tertile. The narrow range of serum 25(OH)D observed in our population could have led to us missing the possible protective effect of higher levels of serum 25(OH)D on thyroid autoimmunity. Further studies in vitamin D-sufficient populations with a wider range of serum 25(OH)D levels are required to substantiate the findings of the current study.

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