THYROID
Volume 21, Number 8, 2011
© Mary Ann Liebert, Inc.
DOI: 10.1089/thy.2009.0200

Relative Vitamin D Insufficiency in Hashimoto's Thyroiditis

Gonca Tamer,[1] Safiye Arik,[2] Ismet Tamer,[3] and Damla Coksert[2]

Background: Vitamin D insufficiency, defined as serum levels of 25-hydroxyvitamin D [25(OH)D3] lower than 30 ng/mL, has been reported to be prevalent in several autoimmune diseases such as multiple sclerosis and type 1 diabetes mellitus. The goal of the present study was to assess whether vitamin D insufficiency is also a feature of Hashimoto's thyroiditis (HT).
Methods: We performed a prevalence case–control study that included 161 cases with HT and 162 healthy controls. Serum levels of 25(OH)D3, calcium, phosphorus, and parathyroid hormone were measured in all 323 subjects.
Results: The prevalence of vitamin D insufficiency in HT cases (148 of 161, 92%) was significantly higher than that observed in healthy controls (102 of 162, 63%, $p < 0.0001$). Among HT cases, the prevalence rate of vitamin D insufficiency showed a trend to be higher in patients with overt hypothyroidism (47 of 50, 94%) or subclinical hypothyroidism (44 of 45, 98%) than in those with euthyroidism (57 of 66, 86%), but the differences were not significant ($p = 0.083$).
Conclusion: Vitamin D insufficiency is associated with HT. Further studies are needed to determine whether vitamin D insufficiency is a casual factor in the pathogenesis of HT or rather a consequence of the disease.

Introduction

Vitamin D enters the human body via two sources: exposure of the skin to sunlight and the diet (1). Solar ultraviolet B radiation (wavelength, 290–315 nm) penetrates the skin and converts 7-dehydrocholesterol to previtamin D3, which is rapidly converted to vitamin D3 (1–5).

Dietary vitamin D comes from natural sources such as wild fresh salmon (800 IU of D3 per 3.5 oz), cod liver oil (700 IU of D3 per 1 tps), or sundried Shiitake mushrooms (1600 IU of D2 per 3.5 oz), from fortified foods such as milk (100 IU of D3 per 8 ox), or from supplements. Vitamin D2 is manufactured through the ultraviolet irradiation of ergosterol from yeast, and vitamin D3 through the ultraviolet irradiation of 7-dehydrocholesterol from lanolin. Both are used as vitamin D supplements, although D2 is the form available by prescription in the United States (5).

Vitamin D made in the skin (D3) or ingested (either D2 or D3) travels in the bloodstream bound to vitamin D-binding protein and reaches the liver where it is converted to 25-hydroxyvitamin D3 [25(OH)D3]. This is the major circulating form of vitamin D, the one measured by clinical laboratories to determine the vitamin D status. Its normal serum range is comprised between 30 and 80 ng/mL. Levels below 30 ng/mL are considered by most scholars indicative of vitamin D insufficiency (3,5). Vitamin 25(OH)D3 is inactive and must be converted in the kidneys to 1,25-dihydroxy vitamin D (1,25(OH)2D3), the biologically active form (5).

The best-characterized action of vitamin D is on the small intestine and the bone. In the small intestine, vitamin D increases the absorption of calcium by increasing the expression of a specific calcium channel. In bone, vitamin D induces the differentiation of preosteoclasts to mature osteoclasts, ultimately promoting removal of calcium and phosphorus from the bone (1–3,5).

In more recent years, the actions of vitamin D have expanded well beyond calcium metabolism. Receptors for vitamin D have been described in lymphocytes and numerous tissues including colon, breast, prostate, and brain. A role of vitamin D has been implicated for cancer, cardiovascular diseases, and autoimmunity.

Directly or indirectly, 1,25-dihydroxyvitamin D controls more than 200 genes, including genes responsible for the regulation of cellular proliferation, differentiation, apoptosis, and angiogenesis (1,2). It decreases cellular proliferation of both normal cells and cancer cells and induces their terminal differentiation (1–3,5–7). 1,25(OH)2D3 inhibits some actions and cytokine production, which is important in developing Hashimoto's thyroiditis (HT). 1,25(OH)2D3 not only inhibits dendritic cell (DC)-dependent T-cell activation, but also

Departments of [1]Endocrinology and Metabolism and [2]Internal Medicine, Goztepe Education and Research Hospital, Istanbul, Turkey.
[3]Department of Family Medicine, Kartal Education and Research Hospital, Istanbul, Turkey.

inhibits the production of T helper (Th) 1 cell cytokines, interferon (IFN)-γ, interleukin-2 (IL-2), and B-cell proliferation and induces B-cell apoptosis as well (8–10).

Considering that HT is one of the classical autoimmune diseases and that no information is available about the vitamin D levels in these patients, we designed the present case–control study to compare serum vitamin D levels between HT cases and healthy controls.

Materials and Methods

Study population

The study included 161 cases with HT (152 females and 6 males) and 162 healthy controls (151 females and 11 males). All subjects were matched on age and gender (Table 1). Patients with liver disorders, renal disorders, diabetes mellitus, metabolic bone disorders, primary hyperparathyroidism, or epilepsy treated by anticonvulsant therapy or on other medications that might alter 25(OH)vitamin D or 1,25(OH)2 vitamin D metabolism and thyroid functions were excluded from the study. Diagnosis of HT was made by determining elevated antithyroid peroxidase and antithyroglobulin antibodies and ultrasound patterns suggestive of HT.

HT cases were classified into three subgroups according to their thyroid function status. Overt hypothyroid patients (OHP, $n = 50$) were those with serum thyrotropin (TSH) $>10\,\mu$IU/mL (reference interval was 0.27–4.2 μIU/mL) and free thyroxine (T4) <0.93 ng/dL (reference interval was 0.93–1.7 ng/dL). Subclinical hypothyroid patients (SHP, $n = 45$) were those with normal serum free T4 and free triiodothyronine levels but with serum TSH levels elevated to the range of 5–20 μIU/mL. Euthyroid patients (EPs) were those with normal free T4 and TSH levels (10). The study was conducted over a period between October 2008 and February 2009 and approved by our institutional ethics committee (approval date and number: 21.02.2008, 44/E). All subjects gave informed consent prior to inclusion in the study.

Laboratory investigation

We determined serum 25(OH)D3 level for vitamin D insufficiency. The key diagnostic test in vitamin D insufficiency is demonstration of a decreased serum 25(OH)D value. The 1,25(OH)2D3 levels may be normal in vitamin D deficiency and insufficiency because of the maximal stimulation of 1α-hydroxylase by the low serum phosphorus and high parathyroid hormone (PTH) levels (11). Different studies have evaluated threshold levels for serum 25(OH)D in relation to bone mineral density, lower extremity function, dental health, risk of fractures, cancer prevention, and incident hypertension (5,12–14). Although Ralston *et al.* have defined vitamin D insufficiency when 25(OH)D3 level is less than 20 ng/mL (14), most of the authors have defined vitamin D insufficiency as 25(OH)D3 level lower than 30 ng/mL (5,12,13). Therefore, we accepted that people have vitamin D insufficiency when their serum 25(OH)D3 levels were lower than 30 ng/mL.

For measuring 25(OH)D3, venous blood samples were collected into plain tubes, serum was separated and stored at -70°C for a week until analysis, and levels of 25(OH)D3 were estimated using a kit 25(OH)2D3-Ria-CT (Bruxelles-Belgium). The treated samples were then assayed using a competitive binding radioimmunoassay technique. Serum PTH levels were measured by electrochemiluminescent immunoassay (Modular Analytics E170; Roche Diagnostics). Other biochemical parameters included in this study were albumin, calcium, and phosphorus. Serum levels of these biochemical parameters were determined according to standard laboratory procedures using the autoanalyzer Olympus 2700. Corrected calcium levels were calculated on the basis of albumin levels.

Statistical analysis

All statistical analyses were made by using the software SPSS for Windows V13.0. Normality of distribution of variables was tested by Shapiro–Wilk and Kolmogorov–Smirnov tests. Subjects were compared for differences in biochemical data according to their thyroid function status by two-tailed Mann–Whitney or Kruskal–Wallis tests for comparison of two or more independent samples. Data are expressed as means $\pm$ SD. A p-value below 0.05 (two tailed) was considered to be statistically significant.

Results

Serum 25(OH)D3 levels of the patients with HT were significantly lower than those of CG ($p < 0.0001$). Prevalence of vitamin D insufficiency in the patients' group was significantly higher than that in CG ($p < 0.0001$) (Table 1 and Fig. 1). Serum PTH levels of the patients with HT were significantly higher than those of CG ($p < 0.0001$). Although serum phosphorus levels of the patients with HT were significantly lower than those of CG, calcium levels were not ($p = 0.04$ and $p = 0.17$, respectively) (Table 1). OHP, SHP, and EP were similar in terms of age and sex distribution (Table 2). Serum 25(OH)D3 levels of OHP, SHP, and EP with HT were significantly lower than those of CG ($p = 0.003$, $p = 0.018$, and

Table 1. Characteristics of Hashimoto's Thyroiditis Cases and Healthy Controls

	HT cases (n = *161*)	*Healthy controls* (n = *162*)	p-*Value*
Age (years)	35.4 ± 7.9	34.3 ± 7.6	0.15
Gender (F/M)	152/6	151/11	0.22
Calcium (μIU/mL)	9.4 ± 0.4	9.4 ± 0.4	0.17
Phosphorus (μIU/mL)	3.5 ± 0.6	3.60 ± 0.5	0.04
PTH (μIU/mL)	56.9 ± 23.9	43.2 ± 14.00	<0.0001
25(OH)D3 level (ng/mL)	16.3 ± 10.4	29.6 ± 25.5	<0.0001
Prevalence of vitamin D insufficiency [n (%)]	148 (91.92%)	102 (63%)	<0.0001

HT, Hashimoto's thyroiditis; PTH, parathyroid hormone.

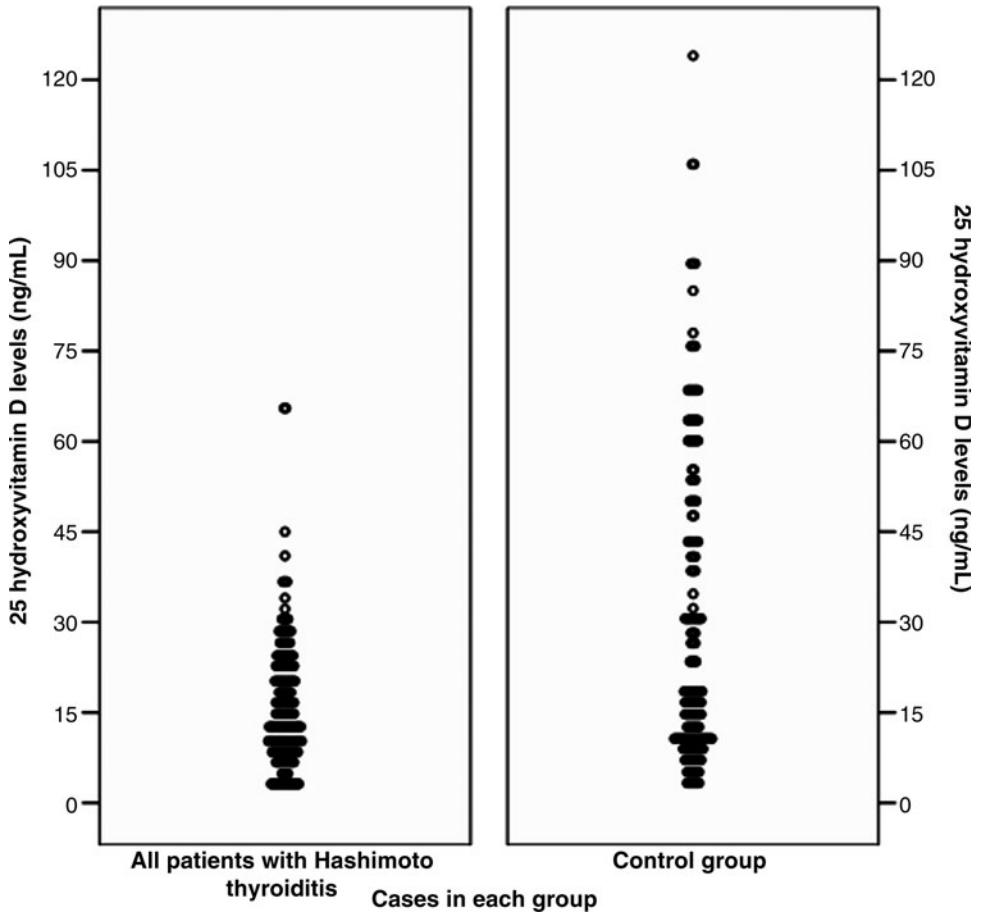

FIG. 1. The individual levels of 25(OH)D_3 in all cases with Hashimoto's thyroiditis and controls.

$p = 0.006$) (Table 3). There were no significant differences among 25(OH)D3 levels of OHP, SHP, and EP with HT ($p = 0.87$) (Table 2).

Rates of vitamin D insufficiency in OHP, SHP, and EP with HT were significantly higher than those of CG ($p < 0.0001$, $p < 0.0001$, and $p = 0.001$, respectively) (Table 3). There were no significant differences among the rates of vitamin D insufficiency in OHP, SHP, and EP with HT ($p = 0.063$) (Table 2). Serum calcium levels of SHP with HT were significantly lower than those of CG ($p = 0.004$) (Table 3), OHP (0.025), and EP ($p = 0.019$). There were no significant differences between serum calcium levels of OHP and EP with HT ($p = 0.34$), between those of OHP and CG ($p = 0.97$) (Table 3), and between those of EP and CG ($p = 0.078$) (Table 3). Serum phosphorus levels of OHP with HT were significantly lower than those of CG ($p = 0.04$) (Table 3). There were no significant differences between serum phosphorus levels of SHP with HT and CG ($p = 0.17$) (Table 3) and between those of EP and CG ($p = 0.28$) (Table 3). There were no significant differences among serum phosphorus levels of OHP, SHP, and EP with HT ($p = 0.61$) (Table 2). Serum PTH levels of OHP, SHP, and EP with HT were significantly higher than those of CG ($p < 0.0001$,

Table 2. Characteristics of Overt Hypothyroidic Patients, Subclinical Hypothyroidic Patients, and Euthyroid Patients with Hashimoto's Thyroiditis

	OHP with HT (n = *50*)	*SHP with HT* (n = *45*)	*EP with HT* (n = *66*)	p-*Value*
Age (years)	36 ± 7.9	35.4 ± 8.9	35.1 ± 7.3	0.903
Gender (F/M)	48/2	43/2	64/2	0.92
Calcium (μIU/mL)	9.4 ± 0.4	9.2 ± 0.5	9.4 ± 0.3	0.03
Phosphorus (μIU/mL)	3.5 ± 0.7	3.5 ± 0.4	3.5 ± 0.5	0.61
PTH (μIU/mL)	61.4 ± 29.2	59.3 ± 22.6	50.9 ± 18.1	0.031
25(OH)D3 level (ng/mL)	15.4 ± 9.3	15.7 ± 7.4	17.4 ± 12.9	0.87
Prevalence of vitamin D insufficiency [*n* (%)]	47 (94%)	44 (97.77%)	57 (86.36%)	0.063

EP, euthyroid patients; OHP, overt hypothyroidic patients; SHP, subclinical hypothyroid patients.

Table 3. Characteristics of Patients' Groups Versus Healthy Controls

	OHP with HT		*SHP with HT*		*EP with HT*		*Healthy controls*
	(n = 50)	p-*Value*	*(n = 45)*	p-*Value*	*(n = 66)*	p-*Value*	*(n = 162)*
Calcium (μIU/mL)	9.4 ± 0.4	0.97	9.2 ± 0.5	0.004	9.4 ± 0.3	0.78	9.4 ± 0.4
Phosphorus (μIU/mL)	3.5 ± 0.7	0.04	3.5 ± 0.4	0.17	3.5 ± 0.5	0.28	3.6 ± 0.5
PTH (μIU/mL)	61.4 ± 29.2	<0.0001	59.3 ± 22.6	<0.0001	50.9 ± 18.1	<0.003	43.2 ± 14
25(OH)D3 level (ng/mL)	15.4 ± 9.3	0.003	15.7 ± 7.4	0.018	17.4 ± 12.9	0.006	29.6 ± 25.5
Rate of vitamin D insufficiency [*n* (%)]	47 (94%)	<0.0001	44 (97.77%)	<0.0001	57 (86.36%)	<0.001	102 (63%)

All *p*-values are vs. control group.

$p < 0.0001$, and $p = 0.003$, respectively) (Table 3). Serum PTH levels of OHP were significantly higher than EP ($p = 0.016$). EPs had the lowest PTH levels in all patients with HT (Table 2); however, their PTH levels were significantly higher than those of CG ($p = 0.003$) (Table 3). There were no significant differences between serum PTH levels of SHP and OHP ($p = 0.53$) and between those of SHP and EP ($p = 0.055$).

Discussion

In the present study, patients with HT had lower 25(OH)D3 levels than healthy subjects and vitamin D insufficiency was more common in patients with HT than in healthy people.

Vitamin D is an important immune system regulator. The active form of vitamin D, 1,25(OH)2D3, has been shown to inhibit the development of autoimmune diseases, including inflammatory bowel diseases. Paradoxically, other immune system–mediated diseases (e.g., experimental asthma) and immunity to infectious organisms were unaffected by 1,25(OH)2D3 (9). Vitamin D receptors (VDRs) are not found in appreciable amounts in the B lymphocyte, but in significant concentrations in the T lymphocyte and macrophage populations (8,13,15). However, their highest concentration is in the immature immune cells of the thymus and mature CD8 T lymphocytes. The significant role of vitamin D compounds as selective immunosupressants is illustrated by their ability to either prevent or markedly suppress animal models of autoimmune disease. The results of the studies show that experimental autoimmune encephalomyelitis, rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes mellitus, and inflammatory bowel disease can be prevented or markedly suppressed by 1,25(OH)2D3 administration (8).

Th1 and Th2 cells responses regulate each other, and during normal immune responses, the host responds with a balance of the two subtypes. Th1 cells secrete IFN-γ, IL-2, and tumor necrosis factor-α, and Th2 cells secrete IL-4 and IL-5, both of which are important for strong antibody-mediated immunity (9,16).

Th1 cell activation is essential for strong cell-mediated immune responses, including host responses to tumors and intracellular pathogens. In autoimmune diseases, Th1 cells are misdirected against self proteins, which results in pathological conditions (9,16).

Th2 cells secrete IL-4 and IL-5, both of which are important for strong antibody mediated immunity. Host responses to extracellular pathogens (bacteria and parasites) require Th2 cells. DCs, Th1, and Th2 cells are direct targets of 1,25(OH)2D3. Quiescent CD4+ T cells express VDRs but only at low concentrations, which increase fivefold after activation (9,16). 1,25(OH)2D3 decreases the proliferation of purified Th cells and decreases the production of IFN-γ, IL-2, IL-5, and tumor necrosis factor-α. In Th2 cells, 1,25(OH)2D3 increases the production of IL-4 (9,16) and transforming growth factor production, which in turn may suppress inflammatory T-cell activity (8). In another study, the effectiveness of 1,25(OH)2D3 for suppression of autoimmune disease *in vivo* was shown to depend on IL-2 (9,17) and IL-4 (9,18) secretion. CD4+ T cells from VDR-knockout (KO) mice (which do not respond to vitamin D) produced more IFN-γ and less IL-2 and IL-5 than did CD4+ cells from wild type (WT). Further, 1,25(OH)2D3 reduced Th1 cell-associated cytokine production and increased Th2-cell IL-4 secretion (19). In the absence of vitamin D signaling, the T-cell compartment has a potentially stronger Th1 phenotype (9,20). Noting VDR in promyelocytes, Abe *et al.* and Tanaka *et al.* have demonstrated that vitamin D can suppress proliferation of promyelocytes and cause their differentiation into monocytes (8,21,22).

Vitamin D or VDR-deficient hosts have elevated Th1-cell associated responses and decreased Th2-cell associated responses. In the absence of VDRs, Th1-cell driven inflammatory bowel disease is more severe and Th2 cell-driven asthma does not develop. The evidence suggests a model in which the effectiveness of 1,25(OH)2D3 treatment of autoimmune diseases results from inhibition of the development and function of Th1 cells and induction of other T cells, including Th2 cells (9,23). Moreover, 1,25(OH)2D3 inhibits DC differentiation and maturation, leading to downregulated expression of MHC-II, costimulatory molecules, and IL-12, enhances IL-10 production, and promotes DC apoptosis. Because of these effects, 1,25(OH)2D3 inhibits DC-dependent T-cell activation (13).

Although vitamin D receptors are not found at appreciable amounts in the B lymphocyte, Chen *et al.* have suggested that vitamin D might play a role in regulating antibody production. They have found that 1,25(OH)2D3 not only inhibits activated B-cell proliferation but induces their apoptosis as well (24).

Hashimoto's disease comprises a cadre of complex diseases with an underlying etiopathology originating from a genetic–environmental interaction, between susceptibility genes (e.g., CTLA-4, HLA-DR, thyroglobulin) and environmental triggers (25,26).

Volpe suggested that HT is predominantly a disorder of cell-mediated immunity that is manifested by a genetic defect in the suppressor T-cell function (27,28). This theory postulates that as a result of defective suppressor T cells, Th (CD4) cells are not suppressed and, therefore, are able to activate and cooperate with B lymphocytes. Additionally, the Th cells produce various cytokines, including IFN-γ, which induces thyrocytes to express major histocompatibility complex class II surface HLA-

DR antigens and renders them susceptible to immunologic attack. Although HLA-DR antigens are not normally expressed on thyroid cells, in HT, the thyroid follicular cells presents HLA-DR antigens on their surface, which may trigger autoimmune process. Activated by T lymphocytes, B lymphocytes produce antibodies that react with thyroid antigens (27,29). Autoantibodies against the TSH receptor molecule on the plasma membrane of the thyroid gland follicles cause a nonphysiological response (30). Patients with HT produce high levels of thyroid autoantibodies and contain lymphoid tissue that resembles secondary lymphoid follicles (31).

In our study, patients with HT had lower 25(OH)D3 levels than the healthy people and prevalence of vitamin D insufficiency was higher in patients with HT than in healthy people. These findings may be resulting from the possible role of vitamin D on the autoimmune processes.

In HT, it is possible that the autoimmune process may be inhibited at different stages by 1,25(OH)2D3. At first, 1,25(OH)2D3 might inhibit DC-dependent T-cell activation (13). Then, 1,25(OH)2D3 might inhibit the secretion of Th1-cell cytokines, IFN-γ, IL-2, and tumor necrosis factor-α. It must be recognized that in HT, immunologic attack is triggered when thyrocytes express major histocompatibility complex class II surface HLA-DR antigens. Production of Th1 cytokines, especially IFN-γ, which induces thyrocytes to express major histocompatibility complex class II surface HLA-DR antigens, might be inhibited by 1,25(OH)2D3. At another stage, after being activated by T cells, B cells' ongoing proliferation might be inhibited and apoptosis might be induced by 1,25(OH)2D3. In this way, 1,25(OH)2D3 might decrease antibodies that react with thyroid antigens (27).

In vitamin D deficiency and insufficiency, serum calcium and phosphorus levels usually decrease and PTH levels usually increase (11,27). In our study, serum PTH levels were significantly higher and serum phosphorus levels were significantly lower in the patients with HT than those of healthy people. But there were no significant differences between serum calcium levels of the patients with HT and healthy people. Serum 25(OH)D3 levels were lower in patients with HT than healthy people, but no difference could be found among serum 25(OH)D3 levels of OHP, SHP, and EP with HT. So, our findings support the idea that there is an association between vitamin D insufficiency and HT and vitamin D insufficiency is more common in patients with HT than in healthy people. But we could not find any significant difference among 25(OH)D3 levels of OHP, SHP, and EP with HT and among the rates of 25(OH)D3 insufficiency in OHP, SHP, and EP with HT.

In conclusion, there may be an association between vitamin D insufficiency and HT. However, there may not be any association between vitamin D insufficiency and progress of thyrocyte damage in HT, as in the present study no significant difference could be found among serum 25(OH)D3 levels of OHP, SHP, and EP with HT and among the rates of vitamin D insufficiency in OHP, SHP, and EP with HT.

Further studies are needed to determine whether vitamin D insufficiency is a casual factor in the pathogenesis of HT or rather a consequence of the disease.

Disclosure Statement

The authors declare that no competing financial interests exist.

References

1. Holick MF 2006 Resurrection of vitamin D deficiency and rickets. J Clin Invest **116:**2062–2072.
2. Holick MF, Garabedian M 2006 Vitamin D: photobiology, metabolism, mechanism of action, and clinical applications. In: Favus MJ (ed) Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 6th edition. American Society for Bone and Mineral Research, Washington, DC, pp 129–137.
3. Bouillon R 2001 Vitamin D: from photosynthesis, metabolism, and action to clinical applications. In: DeGroot LJ, Jameson JL (eds) Endocrinology. W.B. Saunders, Philadelphia, pp 1009–1028.
4. DeLuca HF 2004 Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr **80:**Suppl: 1689S–1696S.
5. Holick MF 2007 Vitamin D deficiency. N Engl J Med **19:** 266–281.
6. Dusso AS, Brown AJ, Slatopolsky E 2005 Vitamin D. Am J Physiol Renal Physiol **289:**F8–F28.
7. Nagpal S, Na S, Rathnachalam R 2005 Noncalcemic actions of vitamin D receptor ligands. Endocr Rev **26:**662–687.
8. Deluca HF, Cantorna MT 2001 Vitamin D: its role and uses in immunology. FASEB J **15:**2579–2585.
9. Cantorna MT, Zhu Y, Froicu M, Wittke A 2004 Vitamin D status, 1,25-dihydroxyvitamin D3, and the immune system. Am J Clin Nutr **80:**1717S–1720S.
10. Li HS, Verginis P, Carayanniotis G 2006 Maturation of dendritic cells by necrotic thyrocytes facilitates induction of experimental autoimmune thyroiditis. Clin Exp Immunol **144:**467–474.
11. Lavin N, Hershman JM 2002 Hypothyroidism and hyperthyroidism. In: Lavin N (ed) Manual of Endocrinology and Metabolism, 3rd edition. Lippincott Williams and Wilkins, Philadelphia, pp 396–409.
12. Lorenzo JA, Canalis E, Raisz LG 2008 Metabolic bone disease. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR (eds) Williams Textbook of Endocrinology, 11th edition. W.B.Saunders, Philadelphia, p 1292.
13. Bischoff-Ferrari HA 2008 Optimal serum 25-hydroxyvitamin D levels for multiple health outcomes. Adv Exp Med Biol **624:**55–71.
14. Ralston SH, Binkley N, Bonen S, Kiel DP, Reginster JY, Roux C, Chen L, Rosenberg E, Santora A 2011 Investigators of FOCUS-D (fosavance vs. standart care—use and study of vitamin D) trial. Calcif Tissue Int **88:**485–494.
15. van Etten E, Mathieu C 2005 Immunoregulation by 1,25-dihydroxyvitamin D3:basic concepts. J Steroid Biochem Mol Biol **97:**93–101.
16. Veldman CM, Cantorna MT, DeLuca HF 2000 Expression of 1,25-dihydroxyvitamin D(3) receptor in the immune system. Arch Biochem Biophys **374:**334–338.
17. Mahon BD, Wittke A, Weaver V, Cantorna MT 2003 The targets of vitamin D depend on the differentiation and activation status of CD4 positive T cells. J Cell Biochem **89:**922–932.
18. Bemiss CJ, Mahon BD, Henry A, Weaver V, Cantorna MT 2002 Interleukin-2 is one of the targets of 1,25-dihydroxyvitamin D3 in the immune system. Arch Biochem Biophys **402:**249–254.
19. Cantorna MT, Mahon BD 2005 D-hormone and the immune system. J Rheumatol Suppl **76:**11–20.
20. Coffman RL, Varkila K, Scott P, Chatelain R 1991 Role of cytokines in the differentiation of CD4+ T-cell subsets *in vivo*. Immunol Rev **123:**189–207.

21. Abe E, Miyaura C, Sakagami H, Takeda M, Konno K, Yamazaki T, Yoshiki S, Suda T 1981 Differentiation of mouse myeloid leukemia cells induced by 1 alpha,25-dihydroxyvitamin D3. Proc Natl Acad Sci USA **78:**4990–4994.
22. Tanaka H, Abe E, Miyaura C, Kuribayashi T, Konno K, Nishii Y, Suda T 1982 1alpha,25-Dihydroxycholecalciferol and a human myeloid leukaemia cell line (HL-60). Biochem J **204:**713–719.
23. Cantorna MT 2000 Vitamin D and autoimmunity: is vitamin D status an environmental factor affecting autoimmune disease prevalence? Proc Soc Exp Biol Med **223:**230–233.
24. Chen S, Sims GP, Chen XX, Gu YY, Chen S, Lipsky PE 2007 Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. J Immunol **179:**1634–1647.
25. Jacobson EM, Huber A, Tomer Y 2008 The HLA gene complex in thyroid autoimmunity: from epidemiology to etiology. J Autoimmun **30:**58–62.
26. Szyper-Kravitz M, Marai I, Shoenfeld Y 2005 Coexistence of thyroid autoimmunity with other autoimmune diseases: friend or foe? Additional aspects on the mosaic of autoimmunity. Autoimmunity **38:**247–255.
27. Jackson IMD, Hennessey JV 2001 Thyroiditis. In: Becker KL (ed) Principles and Practice of Endocrinology and Metabolism, 3rd edition. Lippincott Williams & Wilkins, Philadelphia, pp 456–459.
28. Volpe R 1991 Autoimmune thyroiditis. In: Braverman LE, Utiger RD (eds) Werner and Ingbar's The Thyroid, 6th edition. JB Lippincott Co., Philadelphia, pp 921–941.
29. Bottazzo GF, Pujol-Borrell R, Hanafusa T, Feldmann M 1983 Role of aberrant HLA-DR expression and antigen presentation in induction of endocrine autoimmunity. Lancet **2:**1115–1119.
30. Djurica S, Trbojević B, Milosević DP, Marković N 2005 Autoimmune thyroid disease—clinical symptoms of associated autoimmunity. Srp Arh Celok Lek **133:**16–24.
31. Armengol MP, Juan M, Lucas-Martín A, Fernández-Figueras MT, Jaraquemada D, Gallart T, Pujol-Borrell R 2001 Thyroid autoimmune disease: demonstration of thyroid antigen-specific B cells and recombination-activating gene expression in chemokine-containing active intrathyroidal germinal centers. Am J Pathol **159:**861–873.

Address correspondence to:
Gonca Tamer, M.D.
Department of Endocrinology and Metabolism
Goztepe Education and Research Hospital
Tellikavak sok. No. 8, A blok, D:24
Istanbul 34738
Turkey

E-mail: hgtamer@yahoo.com