

Vitamin D in Thyroid Disorders

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Key words

- vitamin D
- vitamin D deficiency
- calcitriol
- thyroid cancer
- autoimmune thyroiditis
- Graves' disease
- Hashimoto thyroiditis
- hyperthyroidism
- hypothyroidism

Abstract

Vitamin D's canonical role are its effects exerted on the musculoskeletal system. In the last decades the importance of this hormone has been studied in the context of extraskelatal health. Hypovitaminosis D and several polymorphic variants of genes coding proteins crucial in the transport, metabolism and effects of vitamin D have been associated with negative health outcomes.

In this review the current state of knowledge on the role of vitamin D in thyroid disorders is pre-

sented. The review is based on a literature search of the PubMed database performed in December 2014. The following search terms were used in conjunction with 'vitamin D': thyroid cancer, Graves', Hashimoto, thyroiditis, autoimmune thyroid, AITD, nodules, hyperthyroidism, and hypothyroidism.

Currently, similarly to other extraskelatal health outcomes, a clear role of vitamin D has not been demonstrated in thyroid disorders. Further research is necessary to fully elucidate the importance of vitamin D in case of thyroid disease.

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Abbreviations

1,25(OH) ₂ D	1,25-dihydroxyvitamin D, calcitriol
24,25(OH) ₂ D	24,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D, calcidiol
AITD	autoimmune thyroid disease
ATC	anaplastic thyroid cancer
CYP24A1	human gene of cytochrome P450, family 24, subfamily A, polypeptide 1
CYP27B1	human gene of cytochrome P450, family 27, subfamily B, polypeptide 1
CYP2R1	human gene of cytochrome P450, family 2, subfamily R, polypeptide 1
DBP	vitamin D binding protein
DHCR7	human gene of 7-dehydrocholesterol reductase
DIT	diiodotyrosine
DM	diabetes mellitus
DTC	differentiated thyroid cancer
FGF23	fibroblast growth factor 23
FTC	follicular thyroid cancer
GC	human gene of group-specific component (vitamin D binding protein)
GD	Graves' disease
HT	Hashimoto's thyroiditis
Ki67	Ki67 protein

MIT	monoiodotyrosine
MNG	multinodular nontoxic goiter
mRNA	messenger ribonucleic acid
n.a.	not available
NIS	sodium-iodide symporter
PTC	papillary thyroid cancer
RT-PCR	reverse transcriptase polymerase chain reaction
SNP	single-nucleotide polymorphism
TC	thyroid cancer
TG	thyroglobulin
T3	triiodothyronine
T4	thyroxine
TH	thyroid hormones
TPO	thyroid peroxidase
TRAB	anti-TSH-receptor antibodies
TSHR	TSH receptor
TSH	thyroid stimulating hormone
UVB	ultraviolet B
VDR	vitamin D receptor

Introduction

The term 'vitamin D' encompasses several secosteroid compounds; 2 of them, cholecalciferol (or vitamin D₃) and ergocalciferol (vitamin D₂), are

commonly referred to with this name. The former is synthesized in the skin upon exposure to ultraviolet B (UVB) radiation by 7-dehydrocholesterol reductase and acquired from few dietary sources (mainly fatty fish), while the latter is synthesized by plants and fungi, which may constitute vitamin D₂ dietary source for humans.

Both vitamin D₂ and D₃ are hydroxylated in the liver to 25-hydroxyvitamin D (25(OH)D, calcidiol), which is the major circulating and storage form of vitamin D. It has little biological activity, however, its serum concentration is universally acknowledged to reflect vitamin D status (Muscogiuri et al. 2014; Prietl et al. 2013). The active hormone is acquired by hydroxylation of 25(OH)D to 1,25-dihydroxyvitamin D (1,25(OH)₂D, calcitriol). This conversion takes place mainly in the kidney and is regulated by a negative feedback by elevated calcitriol concentrations and fibroblast growth factor 23 (FGF23). However, calcitriol is also synthesized in other cell types (immune cells in particular) as an auto- and paracrine cytokine, without the above regulatory feedback (Prietl et al. 2013). It has been proposed that serum calcidiol level serves as the main determining factor of extrarenal calcitriol synthesis (Jones 2013). Indeed, numerous associations have been found between vitamin D status (reflected by 25(OH)D serum concentration) and extraskeletal health outcomes, rather than with calcitriol serum concentrations (Jones 2013; Holick 2007). Calcitriol inactivation is mediated by 24-hydroxylase. Calcidiol is bound in 88% and calcitriol in 85% with vitamin D binding protein (DBP), 12–15% of circulating vitamin D analytes are bound to albumin, while it is the free form of sterols that has greater accessibility to target cells (Speeckaert et al. 2006). Calcitriol binds most strongly to the intracellular vitamin D receptor, VDR, which acts on response elements of target genes to exert its effects.

A number of polymorphic variants of genes involved in metabolism, transport, and activity of vitamin D have been investigated in recent years. Vitamin D receptor gene's variants have been studied most extensively. Four single-nucleotide polymorphic (SNP) variants of the gene: ApaI, BsmI, FokI, and, TaqI, have been examined most frequently and associated with various health outcomes – among them cancers and autoimmune disorders (Xu et al. 2014; D'Aurizio et al. 2014). Other genes, whose variants may lead to altered availability and metabolism of vitamin D are: DHCR7, GC, CYP2R1, CYP27B1, CYP24A1; they encode proteins mentioned above: 7-dehydrocholesterol reductase, vitamin D binding protein (DBP), 25-hydroxylase, 1- α -hydroxylase, and 24-hydroxylase, respectively.

Calcitriol has been long recognized as a crucial hormone in the regulation of the musculoskeletal system. However, extraskeletal effects of 1,25(OH)₂D have become focus of intense research in the last decade, after establishing the presence of vitamin D receptor in nearly all tissue types (Stocklin and Eggersdorfer 2013; Wacker and Holick 2013). VDR is a transcription factor that conveys the vast majority of biological effects of calcitriol. Also, a form of a membrane-bound vitamin D receptor has been hypothesized, which would mediate non-genomic, rapid effects of 1,25(OH)₂D (Wacker and Holick 2013).

Regarding thyroid disorders, the antiproliferative and prodifferentiating effects of calcitriol come to play in thyroid tumorigenesis, its role in the modulation of the immune system has been pointed out in autoimmune thyroid disease (AITD). Also, in this review the role of vitamin D in the context of thyroid function, hypo- and hyperthyroidism will be presented in brief.

Aim



In this review a summary of the current state of knowledge on the role of vitamin D in thyroid disorders will be presented.

Methods



The review is based on an electronic search of literature in the PubMed database performed in December 2014 using the following search terms: vitamin D thyroid cancer; vitamin D thyroiditis; vitamin D Hashimoto; vitamin D Graves; vitamin D goiter; vitamin D hyperthyroidism; vitamin D hypothyroidism; and vitamin D nodule. Papers were included in the review based on screening of the titles and/or abstracts.

Vitamin D and Thyroid Function



The thyroid gland serves as a synthesis, storage and release organ for the thyroid hormones (THs), thyroxine (T₄) and triiodothyronine (T₃), which are vital for maintaining appropriate function of all tissue and cell types. Their synthesis is stimulated by the thyroid stimulating hormone (TSH) released by the pituitary. Both THs constitute a phenyl ring and a tyrosine molecule; 2 iodine atoms are bound to the tyrosine ring and 2 (in case of T₄) or one (T₃) iodine atom is linked to the phenyl ring (Ross 2015). Only the thyroid gland produces thyroxine, which constitutes approximately 85% of both hormones' secretion, while T₃ is mainly obtained by deiodination of T₄ in peripheral tissues and has a 3- to 8-fold greater biological activity compared to T₄; the latter is considered a prohormone (Szczeklik and Augustynowicz-Kopec 2011). At the microscopic level the thyroid is composed of follicles: follicular cells surround colloid with mostly thyroglobulin (Tg), a glycoprotein that serves as a scaffold for TH production. In brief, iodide – necessary for TH synthesis – is actively taken up into follicular cells by a transmembrane sodium iodine symporter (NIS) located at the cells' basolateral membrane (Ross 2015). Iodide diffuses to the apical (lumen-neighbor) cellular surface, from where it is transferred into the colloid (at least in part by pendrin, an iodide-chloride transporter located in the membrane) (Bizhanova and Kopp 2011). Thyroid peroxidase (TPO) catalyzes oxidation and organification of iodide into tyrosine residues of thyroglobulin, which yields mono- and diiodotyrosine (MIT and DIT, respectively), as well as coupling of 2 DITs into T₄ and one MIT with one DIT into T₃. TH are secreted into extracellular fluid from follicular cells after endocytosis of colloid droplets, which fuse with lysosomes to enable hydrolysis of Tg to T₄, T₃ (and aminoacids constituting the protein) (Ross 2015).

Parafollicular C cells are located among or in the wall of thyroid follicles and they secrete calcitonin in the presence of hypercalcemia. The role of this hormone is probably redundant in humans, since calcium-phosphate homeostasis is affected by neither excessive (i.e., in medullary thyroid cancer patients), nor decreased levels of calcitonin (e.g., in post-thyroidectomy patients) (Clinkspoor et al. 2013).

Clinkspoor and co-authors discussed experimental and clinical data on the role of vitamin D in thyroid function in their review paper. In experiments with rodents: high doses of calcitriol did not alter TSH, nor fT₄ levels in rats; severely vitamin D-deficient

diet led to a decrease in TSH but not fT4; in VDR knock-out mice TSH levels were minimally lower – without alteration in thyroid morphology or function. Further, as mentioned by these researchers (and also to our knowledge) no studies examining the effect of vitamin D on thyroid function have been performed, although basal serum TSH levels in subjects with calcidiol lower than or equal to 10 ng/ml were not significantly different vs. subjects with 25(OH)D of at least 40 ng/ml in a cohort study involving inpatients without thyroid disease history (Clinckspoor et al. 2013). Contrasting results were found for: younger men (lowest age tertile of participants aged 15–98) in a randomly selected Thai cohort of 2582 by Chailurkit, Aekplakorn and Ongphiphadhanakul, as well as for middle-aged and elderly Chinese men in a cohort of 9982 persons by Zhang et al. Data gathered by these research groups indicate an association between higher 25(OH)D and lower TSH levels (Chailurkit et al. 2013; Q Zhang, Wang and et al. 2014).

Hypothyroidism was associated with hypovitaminosis D by Mackawy, Al-Ayed and Al-Rashidi in their study comprising 30 patients and 30 controls. Respective serum 25(OH)D levels were 14.8 and 44.5 ng/ml; a negative correlation between TSH and calcidiol was found: $r = -0.59$ (Mackawy et al. 2013).

On the other hand, Bouillon, Muls and De Moor reported unaltered calcidiol levels in both hypo- and hyperthyroid patients compared to controls ($n=23$, 20 and 81 respectively). In this study calcitriol was also measured: its increased levels were found in hypothyroid (73 pg/ml) patients and decreased in hyperthyroid (28 pg/ml), compared to controls (43 pg/ml). DBP concentration did not differ between controls and hyperthyroid subjects, and in hypothyroid it was just 17% higher, which does not account for calcitriol concentration differences (Bouillon et al. 1980).

Unaltered calcidiol and decreased calcitriol levels in untreated hyperthyroidism patients were also reported by Jastrup and colleagues ($n=25$) as well as MacFarlane and colleagues ($n=21$) (Jastrup et al. 1982; MacFarlane et al. 1982). Enhanced bone turnover leading to secondary hypoparathyroidism explains the change in $1,25(\text{OH})_2\text{D}$.

In regard to parafollicular cells, while in vitro experiments and in vivo studies in rodents demonstrate a negative feedback loop between calcitriol and calcitonin synthesis, important differences exist between humans and rodents in respect to C-cells: in physiological conditions in the former calcitonin is thought to be of no significance. Lack of association between 25(OH)D and calcitonin was shown in the same Belgian hospital patient cohort as mentioned above. After excluding several groups of patients (proton pump inhibitor users, those with renal failure, known thyroid or parathyroid disease) no significant differences were recorded in

calcitonin levels between subjects with low and high vitamin D status (defined as above) (Clinckspoor et al. 2013).

Vitamin D and Thyroid Cancers



Vitamin D status and thyroid cancer

A hypothesis of a protective effect of vitamin D against non-cutaneous cancers has been put forward (Bikle 2014); vitamin D deficiency, reflected by suboptimal calcidiol concentrations, has been proposed as an important cancer risk factor (Wacker and Holick 2013; Pludowski et al. 2013).

In case of thyroid cancers (TCs) specifically, several reports indicate no significant differences in vitamin D status between cancer patients and controls. Laney and colleagues found that 25(OH)D concentrations lower than 30 ng/ml were not different between the following groups: 45 thyroid cancer patients in remission, 24 patients with an active thyroid cancer and 42 thyroid nodule patients. Of note, vitamin D deficiency prevalence in these groups was higher (at 48–58%) than that among healthy controls examined in an earlier study at the same institution (32%) (Laney et al. 2010). Jonklaas, Danielsen and Wang investigated 65 euthyroid patients prior to thyroidectomy (48 with cancer, 17 with a benign thyroid disease) and found that vitamin D status was not associated with a thyroid cancer diagnosis, nor the disease stage among cancer patients (Jonklaas et al. 2013). Lizis-Kolus and colleagues found similar prevalence of suboptimal calcidiol concentrations in 40 female papillary thyroid cancer (PTC) patients and 40 female Hashimoto thyroiditis patients (Lizis-Kolus et al. 2013).

Contrasting data were reported by other groups. Sahin and co-workers recorded vitamin D deficiency (calcidiol < 20 ng/ml) in 71% of PTC patients (166 out of 235), but only in 59% of controls (64/108) (Sahin et al. 2013). Roskies and co-authors reported an association between malignancy and vitamin D deficiency (preoperative calcidiol levels lower than 15 ng/ml) in patients undergoing thyroidectomy at a thyroid cancer center in Montreal: 9 out of 12 differentiated thyroid cancer (DTC) patients were vitamin D deficient compared to 33 out of 88 thyroid nodule patients (Roskies et al. 2012). Kim and colleagues studied 548 women undergoing thyroidectomy for PTC. Among these subjects significantly lower preoperative vitamin D concentrations were found in patients with a tumor sized over 1 cm or with lymph node involvement (Kim et al. 2014). Penna-Martinez and colleagues found an association between DTC and low calcidiol in patients with certain CYP24A1 haplotypes (Penna-Martinez et al. 2012) (◉ Table 1).

Table 1 Studies examining vitamin D status in thyroid cancer patients.

Authors	Study subjects	% female	25(OH)D level [ng/ml]
Laney et al., 2010	TC patients: 24 active, 45 in remission; 42 nodular goiter patients	85	not different between groups
Jonklaas et al. 2013	48 TC and 17 nodular goiter patients	71	not different between groups
Lizis-Kolus et al., 2013	40 PTC and 40 Hashimoto thyroiditis patients	100	not different between groups
Sahin et al., 2013	344 PTC patients and 116 healthy controls	84	17 (PTC) vs. 19.1 (significant)
Roskies et al., 2012	100 patients who underwent total or completion thyroidectomy	87	malignant disease in: 9/12 subjects with 25(OH)D < 15, 33/88 subjects with 25(OH)D ≥ 15
Kim et al., 2014	548 PTC patients who underwent total thyroidectomy	100	significantly lower among patients with tumors > 1 cm or with lymph node metastases

TC – thyroid cancer, PTC – papillary thyroid cancer

In respect to vitamin D supplementation, Zhang and co-authors state in their recent review that conclusive data are not available currently to support a positive or negative effect of supplementing vitamins on thyroid cancerogenesis (LR Zhang et al. 2013; Morand et al. 2014). In contrast, thyroid cancer incidence and mortality has been inversely correlated with solar UVB radiation (Morand et al. 2014; Grant 2008; Grant 2012).

Calcitriol and vitamin D signaling in thyroid cancer

As mentioned above, calcitriol is the active form of vitamin D, which, among all vitamin D forms, exerts the most of biologic effects by binding to VDR. Consequently, the enzymes: 1- α -hydroxylase (CYP27B1), which catalyzes the conversion of calcidiol to calcitriol, and 24-hydroxylase (CYP24A1), calcitriol inactivating enzyme, are crucial in governing the availability of active vitamin D (Clinckspoor et al. 2013). Also, understandably, the effects of calcitriol depend on VDR, whose polymorphic variants have been studied to a limited extent in case of thyroid cancer.

In 3 studies decreased serum 1,25(OH)₂D concentrations in thyroid cancer patients compared to controls were reported. In neither of these did 25(OH)D serum concentrations differ between studied subject population samples (Penna-Martinez et al. 2009; Penna-Martinez et al. 2012; Stepień et al. 2010). The group led by Penna-Martinez found this result by investigating sera of PTC and follicular TC (FTC) patients (132 and 40 respectively in the 2009 study, and, 173 and 38 in the 2012 study) vs. healthy controls (321 and 104, respectively). Stepień and colleagues included 27 PTC, 16 FTC, 7 anaplastic thyroid cancer (ATC), 34 multinodular nontoxic goiter (MNG) patients and 26 healthy volunteers in their study. In all cancer cases calcitriol concentration was decreased, its level was lowest in ATC subjects. Also, 1,25(OH)₂D concentrations were cancer-stage dependent: the more advanced the stage, the lower the concentration (Stepień et al. 2010). The significance of the decreased calcitriol concentration is difficult to interpret taking into account the fact that while in vitro experiments prove antiproliferative effects of the hormone, the doses required to observe these are 2–3 orders of magnitude higher than those recorded in vivo in human blood sera (W Liu et al. 2002; Clinckspoor et al. 2011).

Apart from calcitriol levels, VDR gene polymorphisms were analyzed in the study mentioned above by Penna-Martinez and co-authors. ApaI, TaqI, BsmI and FokI SNPs were investigated. Protection against (i.e., lower incidence of) FTC was associated with alleles AA and FF of the ApaI and FokI polymorphic variants, as well as haplotype tABF, while increased risk for FTC with haplotype Tabf (Penna-Martinez et al. 2009). In another report, Sharma and colleagues treated several lines of thyroid cancer cells with VDR agonists and found that the FF FokI genotype was associated with relative resistance to these chemical compounds (Sharma et al. 2010).

Khadzkou and co-authors reported increased VDR and 1- α -hydroxylase expression in PTC cells compared to normal thyroid follicular cells by immunohistochemical staining of tissue specimens of 35 patients (26 female). Significantly lower VDR immunoreactivity was recorded in PTC metastases. These findings point at a favorable prognosis of PTC provided VDR and 1- α -hydroxylase expression is increased (Khadzkou et al. 2006).

In line with the function of inactivating vitamin D, increased levels of 24-hydroxylase were associated with unfavorable characteristics of thyroid cancer. Zou and colleagues reported that CYP24A1 overexpression indicated a poor prognosis for PTC based on enzyme's gene expression measured by real-time RT-

PCR in tissue specimens of 60 patients (Zou et al. 2014). The same was corroborated by Balla and co-workers who examined CYP24A1 expression by real-time quantitative PCR in normal and cancer tissue sections of 100 patients with PTC: tumor malignancy variables (i.e., vascular invasion, lymph node involvement, tumor size, and hypothyreosis) correlated with CYP24A1 expression (Balla et al. 2014). Resistance to calcitriol (and another VDR agonist) was observed in cells with high baseline 24-hydroxylase mRNA levels by Sharma and co-workers (Sharma et al. 2010). Certain haplotypes of CYP24A1 were associated with decreased calcitriol concentrations in a study by Penna-Martinez and others (Penna-Martinez et al. 2012).

Clinckspoor and colleagues studied protein (by immunohistochemistry) and gene expression (with real-time quantitative RT-PCR) of VDR, CYP24A1 and CYP27B1 in normal thyroid, follicular adenoma and primary thyroid cancer tissue specimens from 72 patients. In DTC and adenoma the 3 proteins' mRNA expression was increased compared to normal thyroid tissue. In PTC tissues of patients who had lymph node metastases VDR and CYP24A1 expression was lower than in specimens from PTC cases without lymph node involvement. ATC tissue specimens often lacked VDR expression and in high mitotic index ATC tumors (Ki67 over 30%) more specimens without VDR, CYP24A1 and CYP27B1 immunoreactivity staining were present (Clinckspoor et al. 2012).

As summarized by this Belgian group in a recent review, data on calcitriol signaling in thyroid cancer to date indicate that local antitumor effects are mediated by this hormone. In thyroid tumors cellular/tissue sensitivity to calcitriol depends on CYP24A1 expression, which may be regarded as a marker thereof. Moreover, in vitro studies on thyroid cancer cell lines have shown antiproliferative and prodifferentiating effects of calcitriol and its non-calcemic analogues (among others by Clinckspoor and co-workers) (Clinckspoor et al. 2013). Further, in vitro experiments with combined calcitriol and other antineoplastic drugs (mainly taxanes) treatment in thyroid cancer cells resulted in additional and/or synergistic effects of the drugs (Clinckspoor et al. 2013). These findings provide perspectives for the possibility of future treatment using VDR signaling in thyroid cancer (◉ Fig. 1).

Vitamin D and Autoimmune Thyroid Disease

Vitamin D modulates the immune system by exerting vital effects on most of its cells. Vitamin D receptor is expressed by

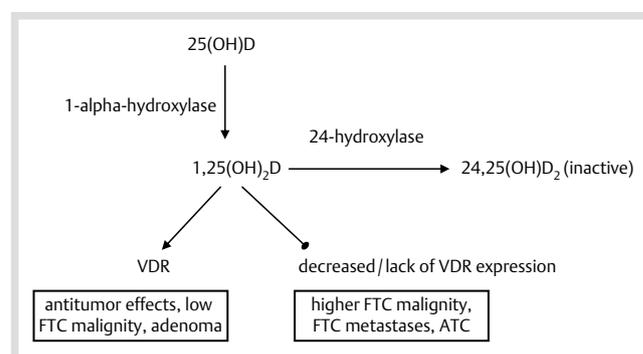


Fig. 1 Local vitamin D signaling in thyroid neoplasms. Studies indicating presented effects are discussed in the text. CYP24A1 expression (gene encoding 24-hydroxylase) in thyroid tumors may be considered a marker of sensitivity to calcitriol. ATC – anaplastic thyroid cancer, FTC – follicular thyroid cancer.

lymphocytes, antigen-presenting cells (e.g., dendritic cells), and macrophages. Calcitriol regulates inflammatory cytokine production and inhibits the proliferation of proinflammatory cells (Yin and Agrawal 2014). The innate immune system is activated by vitamin D, which has been demonstrated by hormone's effect on monocytes and macrophages in particular. An opposite, inhibitory, effect has been shown for the acquired immune response (Bouillon 2014), which results in an enhanced tolerance of this system (Bizzaro and Shoenfeld 2015). The latter immunomodulatory effect of vitamin D has led to investigating its role in a number of autoimmune diseases, which have been associated with hypovitaminosis D (Bizzaro and Shoenfeld 2015; Effraïmidis and Wiersinga 2014). Several observations have been made in regard to autoimmune thyroiditis.

In an animal *in vivo* autoimmune thyroiditis model, CBA strain (general purpose) mice were sensitized with porcine thyroglobulin and treated intraperitoneally with calcitriol at subtherapeutic doses, i.e., 0.1–0.2 micrograms per kg body weight daily. This treatment led to a reduction in the severity of inflammatory lesions in the gland (Fournier et al. 1990). The incidence of thyroiditis was lower in animals which were treated with both calcitriol and cyclosporine A (subtherapeutic doses) (Fournier et al. 1990; Chen et al. 2002). In another study, female Wistar rats, also sensitized with porcine thyroglobulin, were given calcitriol by intraperitoneal injection (5 micrograms per kg every 48 h) prior to or following immunization. In the treated animals the thyroid appeared intact, which contrasted with typical inflammatory changes of the thyroid in the placebo group (S Liu et al. 2010).

Choi et al. reported an association among premenopausal women between lower 25(OH)D levels and AITD (i.e., those with positive anti-thyroid peroxidase, anti-TPO, antibodies) in a cross-sectional study involving approximately 6700 participants aged 25–80, 42% female. Mean calcidiol concentrations were 22 vs. 23.5 ng/ml. This association was not found among postmenopausal subjects. Among all women a trend was also recorded for increasing TPO antibody prevalence and decreasing calcidiol concentrations (12% in subjects with 25(OH)D greater than 30 ng/ml, 15.5% for the 10–20 ng/ml range, 21% in subjects with 25(OH)D lower than 10 ng/ml) (Choi et al. 2014). In a report by Shin and co-workers lower 25(OH)D levels in anti-TPO positive subjects were found, mean values were 12.6 (anti-TPO-positive) vs. 14.5 ng/ml (negative). Further, a weak negative correlation between serum TPO antibodies and 25(OH)D levels ($r = -0.25$) was found by this group among 304 subjects who were enrolled in an endocrinology outpatient clinic (Shin et al. 2014). Unal and colleagues enrolled newly diagnosed Hashimoto's thyroiditis (HT) (254) and Graves' disease (GD) (27) patients as well as age-matched healthy controls. 25(OH)D differed significantly between these 3 groups: 14.9 vs. 19.4 vs. 22.5 ng/ml (Unal et al. 2014). In another study, vitamin D status was compared between endocrine ambulatory AITD patients ($n=50$), non-AITD ones ($n=42$), and healthy age-matched controls ($n=98$). Vitamin D deficiency (25(OH)D level equal to or lower than 10 ng/ml) was found in 72% (79% for Hashimoto's thyroiditis, or HT, 64% for Graves' disease, GD), 52%, and 30% of respective subject groups. Among patients, vitamin D deficiency was more common in those with anti-thyroid antibodies (43 vs. 17%) (Kivity et al. 2011).

On the other hand, after correction for age and sex no correlation was found between calcidiol and anti-TG antibodies among 2582 randomly selected Thai subjects aged 15–98 (Chailurkit et al. 2013; Effraïmidis and Wiersinga 2014). Also, in a community

based study in Delhi where 642 students, teachers and staff were enrolled, only a very weak correlation between serum 25(OH)D and anti-TPO antibody titers was found ($r = -0.08$) after results were adjusted for age (Goswami et al. 2009). In another report, 67 subjects from the Amsterdam AITD cohort, i.e., first- and second-degree relatives of overt AITD patients, developed anti-thyroid antibodies during a 5-year follow-up. However, their vitamin D status did not differ from that of healthy controls. Moreover, in this study, seronegative cohort cases had higher 25(OH)D levels than age-matched controls without AITD family history (Effraïmidis et al. 2012). Furthermore, no significant difference in vitamin D levels was found between 2 DM type 1 patients aged 10–19, i.e., study participants with and without thyroid-specific autoantibodies ($n=19$ for both) (Demir et al. 2014) (☉ Table 2).

The risk of AITD according to VDR gene polymorphisms was summarized in a recent meta-analysis including 8 studies (5 European, 2 Asian, and 1 African). Authors conclude that a decrease in AITD risk is associated with BsmI or TaqI polymorphisms, and, that ApaI or FokI polymorphisms are not significantly associated with AITD risk (Feng et al. 2013; Effraïmidis and Wiersinga 2014).

In a more recent original paper higher frequencies of C alleles of the ApaI polymorphism, and, CC genotype and C allele of the FokI polymorphism were recorded in AITD patients compared to controls (Inoue et al. 2014). Apart from 4 polymorphic variants of the VDR gene, 2 of GC, and one of CYP2R1 were investigated by Inoue and co-authors among 139 Graves' disease, 116 Hashimoto's thyroiditis patients and 76 control subjects. Regarding both diseases: a higher frequency of the C allele for the TaqI VDR polymorphism was found in Graves' compared to Hashimoto's disease patients; and a higher frequency in Hashimoto's compared to Graves' disease patients and controls for the CC variant of the FokI VDR polymorphism (Inoue et al. 2014).

Promoter polymorphism of the CYP27B1 gene was analyzed by Lopez and others. In their study 139 HT and 334 GD patients were enrolled, along with 320 controls. An allelic variation was associated with both autoimmune diseases (Lopez et al. 2004).

In a report by Pani and colleagues, an intron 8 DBP gene polymorphism was associated with Graves' disease but not Hashimoto's thyroiditis. In their study 561 Caucasian-origin individuals (respectively 95 and 92 pedigrees) were genotyped for 3 polymorphisms of the gene (Pani, Regulla, Segni, Hofmann et al. 2002).

Also, as concluded by the same research group, based on their analysis of respectively 106 and 92 patients no association was apparent between CYP1- α intron 6 polymorphism and Graves' disease or Hashimoto's thyroiditis (Pani, Regulla, Segni, Krause et al. 2002).

Vitamin D and Hashimoto's thyroiditis

Regarding vitamin D status and Hashimoto's thyroiditis, Bozkurt and co-workers reported correlations between 25(OH)D concentrations and: thyroid volume ($r=0.15$), as well as anti-TPO ($r = -0.36$) and anti-TG ($r = -0.34$) levels. In their study 180 HT euthyroid patients, 180 newly-diagnosed HT subjects and 180 healthy controls were enrolled. Calcidiol levels lower than 10 ng/ml were recorded in 48.3, 35 and 20.5% of subjects respectively (Bozkurt et al. 2013). In another report, vitamin D deficiency prevalence was significantly higher in children with HT ($n=78$) than in healthy controls ($n=74$), i.e., 73 vs. 17.6%. Patients' calcidiol concentrations inversely correlated with anti-TPO levels

Table 2 Studies examining vitamin D status and autoimmune thyroid disease.

Authors	Study subjects	% female	25(OH)D level [ng/ml]
Choi et al., 2014	cross-sectional study, n=6700	42	22 in anti-TPO(+) vs. 23.5 in anti-TPO(-) premenopausal women
Shin et al. 2014	304 endocrine clinic outpatients	88	12.6 in anti-TPO(+) vs. 14.5 in anti-TPO(-) subjects;
Kivity et al., 2011	50 AITD and 42 non-AITD endocrine clinic outpatients; 98 healthy controls	77	<10 in 79% of HT, 64% of GD, 52% of non-AITD patients, and, 30% of controls
Chailurkit et al., 2013	randomly selected 2582 subjects	50	did not correlate with anti-TG levels
Goswami et al., 2009	642 students, teachers and staff of 4 schools and a medical college	62	not different between anti-TPO(+) and (-) subjects
Unal et al., 2014	newly-diagnosed: 254 HT and 27 GD patients; 124 healthy controls	89	14.9 vs. 19.4 vs. 22.5 (significant); correlated with anti-TPO (r = -0.18) and -TG (-0.14)
Bozkurt et al., 2013	180 newly-diagnosed and 180 euthyroid HT patients; 180 healthy controls	68	<10 in 48%, 35% and 21% of respective subjects; correlated with anti-TPO (r = -0.36) and anti-TG antibodies (-0.34)
Camurdan et al., 2012	78 children with HT, 74 healthy controls	n. a.	deficiency in 73% (patients) vs. 18% (controls); calcidiol correlated with anti-TPO levels among patients (r = -0.3)
Mansournia et al., 2014	41 hypothyroid HT patients and 45 healthy controls	n. a.	was inversely associated with HT (OR: 0.81 for 5 ng/ml increase in 25(OH)D)
Zhang et al., 2014	35 TRAB(+) and 35 TRAB(-) GD patients; 70 healthy controls	60	<20 in respectively 65, 20 and 17% of subjects; correlated with TRAB titer r = -0.5
Yasuda et al., 2013	GD patients: 18 in and 36 not in remission; 49 healthy controls	100	respectively 15.5, 18.2, and 18.6 (significant)
Yasuda et al., 2012	36 newly-diagnosed GD patients; 46 controls	100	14.4 vs. 17.1 (significant); correlated with TRAB titer r = -0.45

GD – Graves' disease, HT – Hashimoto's thyroiditis, n. a. – not available, TRAB – anti-TSH-receptor antibodies, anti-TG – anti-thyroglobulin antibodies, anti-TPO – anti-thyroid-peroxidase antibodies

(r = -0.3) (Camurdan et al. 2012). Mansournia and colleagues enrolled 41 hypothyroid HT patients and 45 healthy controls and reported an inverse association between 25(OH)D concentration and HT risk; the patients to controls ratio of geometric means of calcidiol concentrations was 0.66 (Mansournia et al. 2014).

Concerning VDR genetic variants, in brief, FokI SNP polymorphism was associated with HT in Japanese females (study involved 130 patients and 150 controls) and Taiwanese Chinese subjects (109 HT subjects including 9 men, 90 controls) (Ban et al. 2001; Lin et al. 2006); BsmI polymorphism, BsmI-TaqI bT haplotype, as well as, baT and BaT extended BsmI-ApaI-TaqI haplotypes were associated with HT in a study comprising 145 patients and 145 healthy controls from the Croatian population (Stefanic et al. 2005); TaqI TT and FokI FF genotypes were significantly more common in HT patients (n = 111) than healthy controls (n = 159) in Turkey (Yazici et al. 2013). Results concerning associations between HT and polymorphic variants of other genes vital in vitamin D metabolism were mentioned above.

Vitamin D and Graves' disease

Vitamin D status reported in 35 GD patients with anti-TSH-receptor antibodies (TRABs) was significantly lower than in 35 seronegative GD patients and 70 healthy controls in a study by Zhang, Liang, and Xie. 25(OH)D concentration <20 ng/ml was recorded in respectively ca. 65, 20, and 17% of subjects. An inverse correlation between TRAB titer and 25(OH)D level was found: r = -0.5 (H Zhang and Liang and et al. 2014).

Yasuda and colleagues enrolled female GD patients: 18 in remission (defined as euthyroid status for more than a year after discontinuing anti-thyroid drugs) and 36 without remission (discontinuing ant-thyroid drugs was unattainable 4 years after therapy initiation, TRABs were present), as well as 49 healthy controls (with normal thyroid function, without anti-TPO and -TG antibodies). Mean 25(OH)D levels were 14.5, 18.2, and 18.6 ng/ml (with significant differences), respectively (Yasuda et al. 2013). The same research group also reported a correlation between serum calcidiol level and thyroid volume in newly-

diagnosed female Graves' disease patients (n = 26, all were hyperthyroid and TRAB-positive): r = -0.45. Patients' mean 25(OH)D was significantly lower compared to 46 controls (14.4 vs. 17.1 ng/ml) (Yasuda et al. 2012).

Kawakami-Tani and co-authors performed an intervention study among Graves' disease patients, who were randomly assigned to receive methimazole with or without vitamin D (n = 15 for both groups). Subjects receiving vitamin D achieved euthyroidism faster (Kawakami-Tani et al. 1997). However, far-reaching conclusions cannot be drawn from this report not only due to the small sample size, but also several other methodological restrictions (Rotondi and Chiovato 2013).

Regarding genetic studies, in a meta-analysis from 2009 accumulated data pointed at an association of ApaI, BsmI and FokI VDR gene polymorphisms and GD in Asians, and no association of the ApaI, BsmI, TaqI and FokI variants with GD among Caucasians (Zhou et al. 2009); in an Egyptian population findings were the same as for Asian subjects (Abd El Gawad et al. 2012). In 2 studies DBP gene polymorphisms were associated with GD: results of Pani and co-workers were mentioned above (Pani, Regulla, Segni, Hofmann et al. 2002); Kuryłowicz and colleagues enrolled 332 Polish patients and 185 healthy controls and found that susceptibility to GD was associated with Lys allele at codon 420 of this gene (but not with the codon 416 SNP nor variable repeat (TAAA)N polymorphism in intron 8), which also correlated with lower calcidiol concentration (Kuryłowicz et al. 2006). In a study mentioned above, Inoue and colleagues also noted lower frequencies of one genetic variant of the GC and one of the CYP2R1 gene in intractable GD patients (Inoue et al. 2014). In a Polish population comprising 326 patients and 175 controls, Kuryłowicz and Badenhop reported an association with GD of the same CYP27B1 gene promoter SNP (1260 C) as Lopez and colleagues (Kuryłowicz and Badenhop 2005; Lopez et al. 2004).

Vitamin D and postpartum thyroiditis

Krysiak, Kowalska and Okopień studied 4 groups of non-lactating women: hypothyroid (n = 14) and euthyroid (n = 14) subjects with postpartum thyroiditis, participants with non-autoim-

mune hypothyroidism (n=16), and an euthyroid group without thyroid autoimmunity (n=15). Serum 25(OH)D concentrations among thyroiditis patients were lower than in the remaining subjects, as well as lower in hypo- than euthyroid women (respective means of the 4 groups: 18, 30, 38 and 53 ng/ml). Further, anti-TPO and anti-TG antibody titers correlated with calcidiol levels (r coefficients in the range of -0.22 to -0.34). Hypothyroid subjects were treated with L-thyroxine, however, researchers observed an increase in calcidiol levels only in post-partum thyroiditis patients (thyroid function improved in both groups that required treatment). A correlation between 25(OH)D levels after thyroxine treatment and antibody titers was recorded too (r=-0.3 and -0.2 for respectively anti-TPO and anti-TG). Authors mention the major limitations of their results, among them the low number of subjects, no significant difference in calcidiol levels between groups after taking into account the season of sample collection (Krysiak et al. 2014).

Conclusions

The importance of extraskeletal effects of vitamin D have been studied extensively (Bouillon 2014; Schottker et al. 2013; Pludowski et al. 2013; Wacker and Holick 2013). As can be drawn from this review, research on vitamin D and thyroid disorders too has underlined hormone's significance – particularly in case of gland's cancers and autoimmune diseases. Still, in many points accumulated data are inconclusive, many unresolved questions remain, therefore, it remains necessary to perform further studies that would affect clinical approaches to thyroid disease. Studies demonstrating associations of hypovitaminosis D with AITD and basic research rationale underlying this relation might lead to recommendations of vitamin D supplementation for the patients, however, currently such treatment is still controversial (Bizzaro and Shoenfeld 2015). Also, at this point, clinical choices are not dependent on possible associations between thyroid disease and genetic variants of VDR and other proteins important in vitamin D metabolism and transport. Applying antineoplastic effects of calcitriol in a clinical setting remains a possible future perspective. Currently, in the context of thyroid disease, but also in a broader perspective, no highly convincing data for any health outcome are available. Moreover, vitamin D supplementation has not affected disease occurrence in intervention studies, as summarized in 2 recent reviews. The associations between vitamin D deficiency and disease may indicate that 25(OH)D is only a marker of ill health (Theodoratou et al. 2014; Autier et al. 2014).

Conflict of interest: None.

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