



Vitamin D, Thyroid Hormones and Cardiovascular Risk: Exploring the Components of This Novel Disease Triangle

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The role of thyroid hormones (THs) in the cardiovascular (CV) system, through several direct and indirect effects is recognized. Even very small modification in TH levels (as those observed in subclinical hypothyroidism or hyperthyroidism, and low triiodothyronine syndrome) may adversely affect the CV system, whereas thyroid hormones benefit the CV system and improve the prognosis. There is also evidence of vitamin D effects on cardiometabolic disease (e.g., through modulation of endothelial and smooth muscle cell activity, renin-angiotensin-aldosterone system, nitric oxide, oxidative stress, and inflammatory response), as well as an association between vitamin D [25(OH)D] deficiency and autoimmune thyroid diseases or cancer, and a relationship between vitamin D concentration and titers of antibodies and thyroid autoimmunity replacement. Interestingly, experimental data indicate a direct effect of vitamin D on Type 2 deiodinase expression causing subsequential peripheral conversion of T4 into T3. However, the functional links among THs, vitamin D and the cardiovascular system, and clinical effects of coexisting abnormalities in this new troublesome triad, have not yet been reviewed. The main aim of this review is to discuss pathophysiology of this relationship, proposing new mechanistic insights involving vitamin D in the modulation of cardiometabolic disease and thyroid profile.

Keywords: vitamin D, 25(OH)D, thyroid hormones, cardiovascular system, pathophysiology

INTRODUCTION

The roles of thyroid hormones (THs) in cardiovascular (CV) disease, such as heart failure (HF) or acute myocardial infarction (MI), through several direct and indirect effects are well-known (Jabbar et al., 2017; Abdel-Moneim et al., 2020). The two conditions share a number of underlying mechanisms and risk factors (e.g., endothelial dysfunction, increased blood pressure and dyslipidemia) (Jabbar et al., 2017). Moreover, the importance of THs in CV homeostasis may be deduced by the fact that even very small changes in TH levels (e.g., those observed in subclinical hypothyroidism or hyperthyroidism, and low triiodothyronine syndrome) adversely impact the CV system, whereas THs benefit the CV system and improve the prognosis (Razvi et al., 2018; Mastorci et al., 2020). Moreover, whether experimental studies suggest that TH administration may reduce

infarct size and improve myocardial function after acute myocardial infarction (AMI), increasing clinical evidence which indicates that the manifestations of subtle thyroid abnormalities (e.g., low T3 syndrome) during AMI course are associated with adverse prognosis (Razvi et al., 2018).

In this context, the classical roles of vitamin D are related to the regulation of bone turnover and phospho-calcium homeostasis (Caprio et al., 2017). However, the pleiotropic roles of vitamin D have been recognized through preclinical and observational studies, and the importance of vitamin D in non-skeletal sites has emerged, as well as the role of vitamin D in type 2 diabetes (T2D) and cardiovascular and autoimmune diseases, neoplasia, and all-cause mortality (Caprio et al., 2017). Many data indicate that Vitamin D affects cardiometabolic disease. Its actions include modulation of endothelial and smooth muscle cell activity, renin-angiotensin-aldosterone system (RAAS), insulin, nitric oxide, oxidative stress status, inflammatory response, as well as aortic valve calcification processes (Kim et al., 2017; Latic and Erben, 2020; de la Guía-Galipienso et al., 2020). Its deficiency has been associated with CV risk, a higher risk of atherosclerosis, HF and CV mortality (Latic and Erben, 2020; de la Guía-Galipienso et al., 2020).

Moreover, there are some evidence suggesting an association between vitamin D [25(OH)D, the form by which vitamin D status is measured in blood] deficiency and autoimmune thyroid diseases (e.g., Hashimoto's thyroiditis and Graves' disease, and/or postpartum thyroiditis), and a relationship between vitamin D levels and titers of antibodies and thyroid autoimmunity replacement (Kim, 2017). Experimental results suggest that vitamin D status could exert a role on thyroid cancer onset and progression, and that the active form of vitamin D [1,25(OH)2D3] might be beneficial in thyroid cancer treatment (Kim, 2017). Interestingly, vitamin D has been shown to be associated with an increase of Type 2 deiodinase (DIO2) levels and peripheral conversion of THs (specifically from thyroxine-T4 into triiodothyronine-T3) in tissue homogenates (from liver, kidney, muscle, femur bone, heart and brain) of diabetic rats (Alrefaie and Awad, 2015). Moreover, although all the mechanisms underlying the role of vitamin D on TH profile are not completely understood, likely there may be the involvement of vitamin D-related antioxidants, anti-inflammatory and immunoregulatory effects (Kim, 2017).

The functional links among THs, vitamin D and the cardiovascular system, and clinical effects of coexisting abnormalities in this new troublesome triad, have not yet been reviewed. The main aim of this review is to discuss pathophysiology of this triangle, proposing new mechanistic insights involving vitamin D in the onset and development of cardiometabolic disease and TH function.

THs AND CV SYSTEM

TH system has a central regulatory role on virtually all metabolic functions in the human body by interacting with several cellular pathways, TH facilitate the functional integration

among different organs and systems, in various physiological and pathological conditions, involving autonomic nervous system, the renin-angiotensin-aldosterone system, vascular reactivity and renal function (Razvi et al., 2018). At CV level, TH regulate homeostasis mainly by influencing cardiac contractility and systemic vascular resistance. In chronic diseases, at systemic level, TH promote regenerative and reparative processes to compensate the systemic stress conditions (Sabatino et al., 2014). In this perspective, TH play as multiple level regulators and, thus, have a relevant potential for innovative therapeutic approaches (Pantos et al., 2007b, 2010). T3 is considered the biologically active form of TH and mediates almost all TH effects at tissue level. T3 is generated by 5'-monodeiodination of T4 in peripheral tissues by type I (DIO1) and DIO2 deiodinases. A third enzyme, called type III 5-monodeiodinase (DIO3) is responsible of TH catabolism and catalyzes the removal of one iodine from the inner tyrosilic ring of T4 and its conversion to the inactive rT3 (reverse-T3) (Bianco and da Conceicao, 2018). THs homeostasis in the heart requires a fine regulation, involving specific transporters at plasma membranes (such as the monocarboxylate transporters MCT8 and MCT10) (Friesema et al., 2008). The finding of monodeiodinases activities in normal and pathological myocytes unveiled a more complex TH regulatory dynamic than initially thought, since it suggested that both hormones (not only the active T3) can be uploaded inside the cardiac cells by membrane transporters (Sabatino et al., 2000; Gereben et al., 2008). THs effects at genomic level are mediated by specific receptors (TRs): TR α (TR α 1, TR α 2), TR β (TR β 1, TR β 2): TH-TR complex specifically interacts with TH-response elements (TREs) in the promoters of target genes (Cheng et al., 2010). Differently, the non-genomic action of TH trigger specific metabolic pathways involving receptors at plasma membrane level (i.e., integrin α v β 3) or cytosolic TRs (Pantos and Mourouzis, 2014). Recently, the protective effects of THs have been investigated in rats where the alteration of molecular function and biological processes turned out to be beneficial after MI (Pantos et al., 2007a). THs has been shown to increase cardiac contractility, stimulate cardiac hypertrophy and angiogenesis, reduce apoptosis, improve left ventricular remodeling and function. More specifically, T3 regulates myocardial contraction/relaxation in MI by inducing the pathological switch of myosin heavy chains (MHC) from α to β isoform, and controls calcium ions (Ca²⁺) flux into the sarcoplasmic reticulum by inducing expression of sarcoplasmic reticulum calcium adenosine triphosphatase (SERCA2) and inhibiting phospholamban (PLB), SERCA's counteracting molecule (Kinugawa et al., 2001). Interestingly, the overexpression of TR α 1 during the pathological hypertrophy settlement in MI in rats is strictly associated to this receptor redistribution from nucleus to cytoplasm, where it plays an important role in the (MHC) from α to β isoform switch (Kinugawa et al., 2001).

Besides the effects on the heart, TH genomic and, mainly, non-genomic effects are also evident on the vasculature, both in vascular smooth muscle (VSMC) and endothelial cells (Ojamaa et al., 1996; Sabatino et al., 2015). The rapidity with which VSMC respond to T3 suggest the

involvement of main non-genomic mechanisms, since the genomic would require a longer period for protein synthesis and for biological effects to be observed (Ojamaa et al., 1996). It is well known that T3 induces vascular relaxation via endothelium-dependent pathways. However, more recently, several studies have demonstrated that T3 may potentiate vascular relaxation also through endothelium-independent mechanisms, in which VSMC are a crucial target for T3-mediated vasodilation (Samuel et al., 2017). More specifically, nitric oxide (NO) production by VSMC, other than by endothelium, has been considered the driving factor in local regulation of vascular response (Lee et al., 2008) mainly via PI3K/Akt signaling pathway activation (Carrillo-Sepúlveda et al., 2010). Furthermore, it has been observed that both T4 and T3 administration induce new blood vessel formation via surface receptor $\alpha v\beta 3$ -mediated pathway in human microvascular endothelial cells (Balzan et al., 2013; Liu et al., 2014) and in rat heart and aorta tissues during ischemic reperfusion procedure (Sabatino et al., 2016).

VITAMIN D AND CV PATHOPHYSIOLOGY

Vitamin D receptors are present in a variety of cells and tissues, including cardiomyocytes, VSMC and endothelial cells, suggesting many extra-skeletal effects of this vitamin, over the traditional calcium and phosphorus homeostasis (Gouni-Berthold and Berthold, 2021). Indeed, several data reported a correlation between vitamin D deficiency and CV disease, as 25(OH)D levels appeared associated with different CV risk factors (e.g., blood pressure, obesity, and metabolic syndrome), incidence of atherosclerosis and heart failure, peripheral arterial disease, and adverse prognosis and mortality, suggesting that the indirect association between hypovitaminosis D with the cardiovascular system is essentially explained through its association with cardiometabolic risk factors (Vassalle et al., 2015). In particular, the effects of vitamin D on diabetes include improvement of insulin sensitivity (e.g., through modulation of adiponectin gene), increase of insulin gene transcription, insulin receptor expression, and glucose transport (Maestro et al., 2000; Lahbib et al., 2015; Lontchi-Yimagou et al., 2020). In humans, 25(OH)D inversely correlates with glycated hemoglobin, and with prevalence and risk of diabetes (Zhao et al., 2020; Bejar et al., 2021; Salih et al., 2021).

Over the course of time, it has been estimated that calcitriol directly or indirectly regulates a myriad of genes, modulating a number of pathophysiological pathways. Both genomic and non-genomic actions are mediated by the vitamin D receptor (VDR), through regulation of transcriptional activity of target genes or activation of intracellular second messengers (Pike et al., 2016). Nonetheless, the modulation of gene expression may be regulated by co-regulatory elements rather than only by VDR (Pike et al., 2016). Thus, it is difficult to list all possible effects mediated by vitamin D on the CV system. In fact, many possible mechanisms may explain effects of vitamin D on CV systems through effects on endothelium (e.g., vitamin D deficiency causes reduced eNOS expression and SOD activity), smooth muscle cells

and vascular calcification (e.g., modulating metalloproteinase expression), RAAS activation, effects on altered inflammatory pathways (e.g., vitamin D deficiency is associated with increased of NF- κ B and IL-6), insulin secretion and sensitivity (e.g., reducing inflammation and oxidative stress, and regulates Ca^{2+} level in different cellular types as well as adipokines release such as adiponectin and leptin), parathyroid hormone (PTH) secretion [1,25(OH)2D regulates its own synthesis decreasing the PTH synthesis and secretion] (Jablonski et al., 2011; Aoshima et al., 2012; Szeto et al., 2012; Vassalle and Pérez-López, 2013; Wacker and Holiack, 2013; Lim et al., 2020; Szymczak-Pajor et al., 2020; Wee et al., 2021) (**Figure 1**).

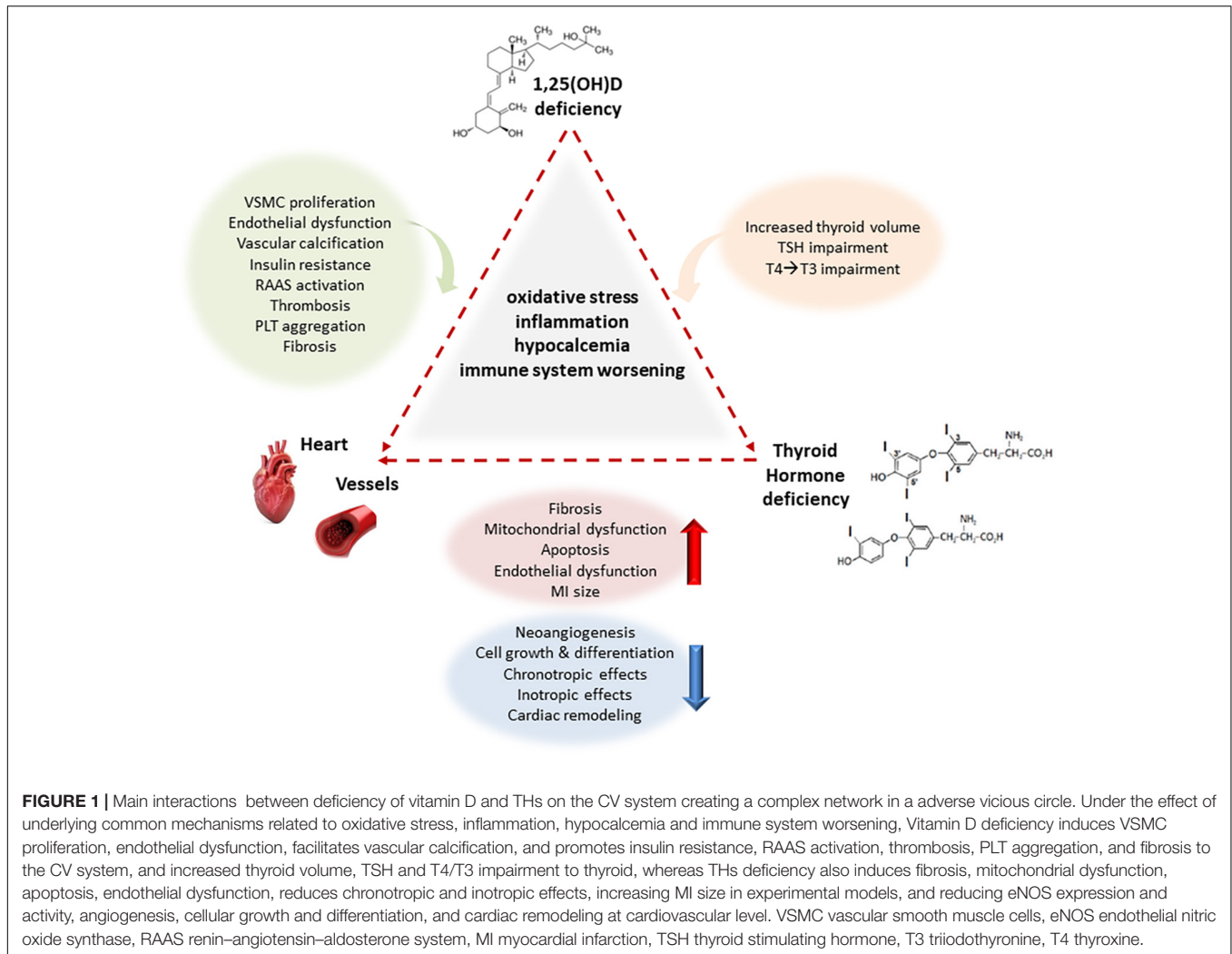
Chronic vitamin D deficiency may predispose to hypertension, and one mechanism recently identified characterizing this direct cardiac effects is the modulation of the function of transient receptor potential C cation channels, which is a mechanosensitive cation channel that plays a role in cardiac slow-force responses to hemodynamic changes (Stratford et al., 2021). Moreover, vitamin D has direct effects on the atrial electrophysiology and atrial fibrillation, a direct association with regulation of cardiac autonomic activity, and a direct role in the regulation of vasomotor inducing changes of pressor and depressor vasomotor responses (Mann et al., 2013; Hanafy et al., 2014). Some studies evidenced that vitamin D deficiency results in structural and ionic channel remodeling and autonomic dysfunction that may predispose the individuals to lethal cardiac arrhythmias and sudden cardiac death (Drechsler et al., 2010; Deo et al., 2011; Mann et al., 2013). In fact, vitamin D has direct effects on myocytes. Vitamin D also affects cardiac contractility indirectly by calcium metabolism and directly via vitamin D receptors-VDR (Tishkoff et al., 2008).

For it concerns atherosclerosis, vitamin D can act in several ways. For example, macrophages lacking VDR present an increase in the uptake of cholesterol and this results in cholesterol accumulating in the intracellular space, whereas knockdown of VDR in endothelial cells leads to endothelial cell activation (upregulation of VCAM-1, ICAM-1 and IL-6, decreased peripheral blood mononuclear cell-PBMC rolling velocity and increased PBMC rolling flux and adhesion to the endothelial line) (Szeto et al., 2012; Bozic et al., 2015).

Interestingly, among direct effects, recent data suggest that vitamin D maintains endothelial stability *in vitro* by enforcing cell-cell interactions (Vila Cuenca et al., 2018).

However, although several studies have demonstrated beneficial effects of vitamin D supplementation (versus placebo) on CV clinical manifestation and risk factors, no clear benefit of vitamin D administration for CV disease has been evidenced in randomized controlled trials (Latic and Erben, 2020; Michos et al., 2021).

Surely further work is needed to establish the protective role of vitamin D in this setting, as controversial results may be due to interference of possible confounding factors, such as baseline 25(OH)D levels, dose, duration of supplementation, season, as well as population characteristics (e.g., number of subjects enrolled, heterogeneity of patients, time spent outdoors), which may be considered in result interpretation.



VITAMIN D AND THYROID PATHOPHYSIOLOGY

The finding relative to homology between the vitamin D receptor (VDR) and the TH receptor dates back to the late 1980s (McDonnell et al., 1988). Few years later, the VDR expression on rat follicular thyroid cells was evidenced, suggesting a possible vitamin D role in thyroid pathophysiology (Berg et al., 1994). However, until today, most data that evaluated the role of vitamin D in thyroid illnesses are only in the context of autoimmunity and cancer (recently reviewed in Kim et al., 2017; Mele et al., 2020).

Autoimmune Thyroid Disease (AITD)

Hypovitaminosis D appears involved in the pathogenesis of autoimmune disease, where the most common autoimmune thyroid diseases are Hashimoto's thyroiditis (HT) and Grave's disease (GD).

Hashimoto's thyroiditis (HT) is characterized by lymphocytic infiltration destroying the gland tissue, inflammation, and

release of thyroid antibodies (TPOAb and TgAb), leading to hypothyroidism.

A meta-analysis [including 6/3 studies with continuous/dichotomous 25(OH)D levels] showed that HT patients had lower values compared to controls, and more likely have 25(OH)D deficiency (Wang et al., 2015). Moreover, data on the inverse correlation between vitamin D values with thyroid volume, and duration and severity of HT, and TH and thyroid antibody levels further reinforcing the idea that vitamin D deficiency might play a role in the risk, onset and development of HT (Muscogiuri et al., 2016; Chao et al., 2020).

Interestingly, several polymorphisms in the VDR gene (e.g., the most common *BsmI*, *FokI*, *TaqI*, and *ApaI*) have been studied in their association with HT risk (O'Grady et al., 2014; Giovanazzo et al., 2017; Wang et al., 2017). Although the results are controversial and far from definitive, these data suggested the genetically determined low vitamin D might be associated with an increased risk of developing HT.

All together these data suggested the possibility of the use of vitamin D supplementation against HT. Much still needs to be done in this context, because available data retain many pitfalls, as

the study populations are generally small, patients heterogeneous, there is variability of administration (*e.g.*, dose and timing of supplementation), and many confounding factors may affect final results (*e.g.*, age, gender, obesity, lifestyle, baseline vitamin D status, univocity of categories to define hypovitaminosis, season) are often neglected. Moreover, if values higher than 30 ng/mL (75 nmol/L) are considered optimal for bone and mineral homeostasis health, correct levels to lower the risk of autoimmune disease onset and progression are largely unknown (Holick et al., 2011). However, to testify to this possibility, reduction of TPOAb and TgAb levels after cholecalciferol supplementation was observed in patients with low vitamin D (Simsek et al., 2016; Krysiak et al., 2018; Wang et al., 2018).

Grave's disease (GD) is characterized by the presence of gland infiltration by T lymphocytes, thyroid stimulating hormone (TSH) receptor autoantibodies (TRAb), goiter, and ophthalmopathy, and hyperthyroidism.

Two meta-analyses suggested that a low vitamin D status may increase the risk of GD (Wang et al., 2015; Xu et al., 2015). Moreover, there is data on the association between low vitamin D levels and the thyroid autoantibody titre in patients with Graves' disease as well as the association of polymorphisms in the vitamin D receptor (VDR) gene in patients with GD (Unal et al., 2014; Zhang et al., 2015; Veneti et al., 2019; Płazińska et al., 2020).

For it concerns vitamin D supplementation, there are a few studies in the GD setting. In one study, GD patients treated with standard therapy combined with calcitriol [methimazole 30 mg/d supplemented with 1.5 micrograms α (OH)D₃ for 24 weeks] showed a greater decrease in serum FT₄ and FT₃, although there were no differences in TRAb levels compared to those taking only methimazole (Kawakami-Tani et al., 1997). Interestingly, a recent study suggested that administration of cholecalciferol (1000–2000 IU/day) in GD patients with hypovitaminosis D, if not decrease the recurrence rate within one year, determines an earlier occurrence in the group of GD patients not taking cholecalciferol (Cho and Chung, 2020).

Thyroid Cancer

Vitamin D seems to play a critical role in thyroid cancer onset and progression, acting with effects on a number of cellular pathways, including apoptosis, cellular proliferation and differentiation, angiogenesis, oxidative stress and inflammatory response (Mele et al., 2020). However, despite the strong evidence observed in experimental models, clinical studies give more uncertain results (Mele et al., 2020). Nonetheless, two recent meta-analyses evidenced the association between low vitamin D levels and increased risk for thyroid cancer (Hu et al., 2018; Zhao et al., 2019). Instead, more unclear are the studies investigating the role of vitamin D supplementation in preventing thyroid cancer onset, which remain inconclusive (Zhang et al., 2013; O'Grady et al., 2014).

Central and Peripheral Effects on Thyroid Function

Little is known on the relationship between vitamin D to other thyroid dysfunction or disease.

It has been observed that Vitamin D may affect FRTL-5 cells (thyroid *cell* line established from normal thyroid glands in rats) inhibiting TSH-stimulated adenyl cyclase activity, iodide uptake and cell growth (Berg et al., 1994). Moreover, vitamin D₃ administration decreased TSH values toward normal in diabetic rats (52 ± 13 , 70 ± 19 , 57 ± 19 μ IU/ml in control group, diabetic group and diabetic group treated with vitamin D₃, respectively) (Alrefaie and Awad, 2015). Accordingly, an inverse correlation between 25(OH)D levels and TSH was observed in general human populations (Chailurkit et al., 2013; Barchetta et al., 2015).

A central effect of 1,25(OH)₂ vitamin D₃ has been observed in the receptor modulation (VDR) of TSH secretion by rat pituitary thyrotroph cells (Sar et al., 1980; Smith et al., 1989). In this context, experimental data suggested that vitamin D could increase TRH-induced TSH secretion by pituitary thyrotroph cells (D'Emden and Wark, 1987). Despite these effects, it is also possible that the inverse low TSH in the presence of a high vitamin D could be due, almost in part, to increased THs caused by the stimulatory effect of vitamin D on thyrocytes, and the consequent negative feedback control that the THs exert over the hypothalamus and anterior pituitary, thus controlling the release of both thyrotropin releasing hormone (TRH) and TSH (Dietrich et al., 2012; Veneti et al., 2019).

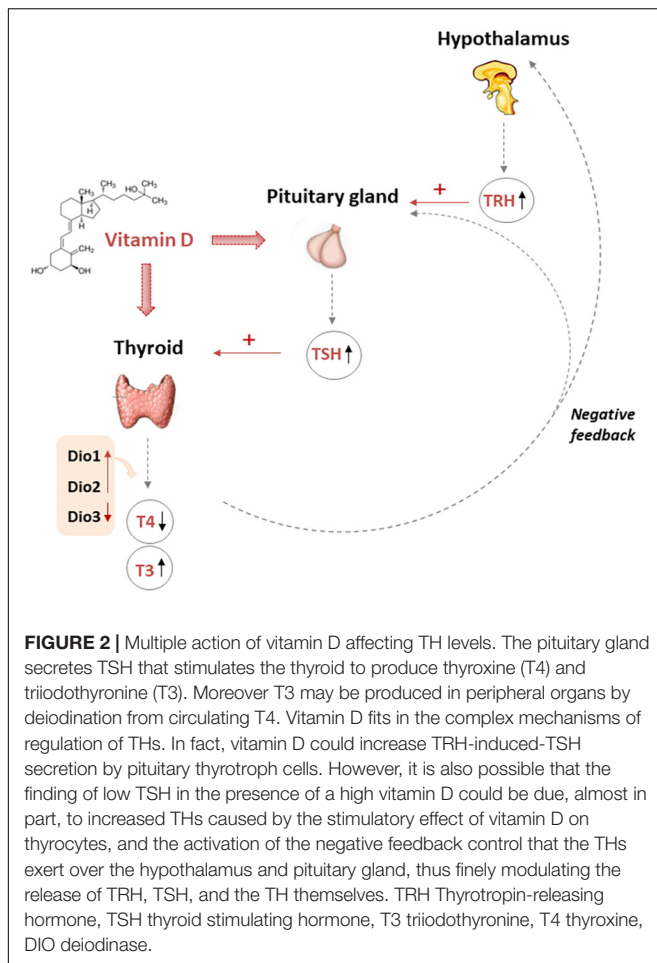
Interestingly, vitamin D administration improved TH profile in diabetic rats, increasing DIO₂ (Alrefaie and Awad, 2015). This effect of vitamin treatment was also observed in bone extracts from mice skeleton, where DIO₂ activity appeared increased by 2 to 3-fold, and in primary osteoblastic cells, where 1,25(OH)₂D₃ dose- and time-dependently induced the mRNA expression of DIO₂ (Miura et al., 2002; Gouveia et al., 2005).

All together these data suggested how vitamin D may be important, acting at central level for pituitary gland function, also modulating DIO₂ expression at thyroid and other organ levels and consequently affecting peripheral conversion of T₄ into T₃ (Figure 2).

However, if is true that vitamin D may affects thyroid pathophysiology, this relationship is likely reciprocal, although less is understood on the influence of THs on vitamin D metabolism. It is known that excess of THs stimulates bone resorption, increasing the blood values of calcium and phosphorus and suppressing PTH secretion whereas in hypothyroidism the bone turnover is decreased, the serum calcium concentration tends to be lower, and PTH secretion activated (Delitala et al., 2020; Hans and Levine, 2021). Accordingly, some data suggested that THs can affect vitamin D metabolism and, consequently, modulate the availability of its active form 1,25-(OH)₂D₃ (decreased in the serum of hyperthyroid patients and increased in the serum of untreated hypothyroid patients), which appeared normalized upon restoration of normal thyroid function (Bouillon et al., 1980).

VITAMIN D IN THE RELATIONSHIP BETWEEN THYROID AND CV SYSTEM

In GD patients, a significant reduction of pulse wave velocity (PWV, index of arterial stiffness, recognized as a CV risk



factor) was observed among vitamin D insufficient participants after cholecalciferol supplementation (70 µg/day-2800 IU for 9 months; Grove-Laugesen et al., 2019). Other results suggested a role for hypovitaminosis D through actions on visceral fat and insulin resistance in the interaction between THs and metabolic syndrome, with consequently increase of cardiometabolic risk (Verrusio et al., 2019). Moreover, an interaction between vitamin D, insulin resistance and thyroid profile dysfunction was observed in obese subjects, likely driven by systemic inflammation, where vitamin D deficiency represented the only independent factor associated with presence of HT in such patients (Răcăţianu et al., 2018). Another study, conducted in a general population, suggested that different combinations of vitamin D and TH status can modulate changes in the lipid profile (triglycerides and HDL) (Mansorian et al., 2018). Clearly, the verification and identification of these correlations as causality relations is required, with the design of interventional or cohort studies to provide benchmark evidence.

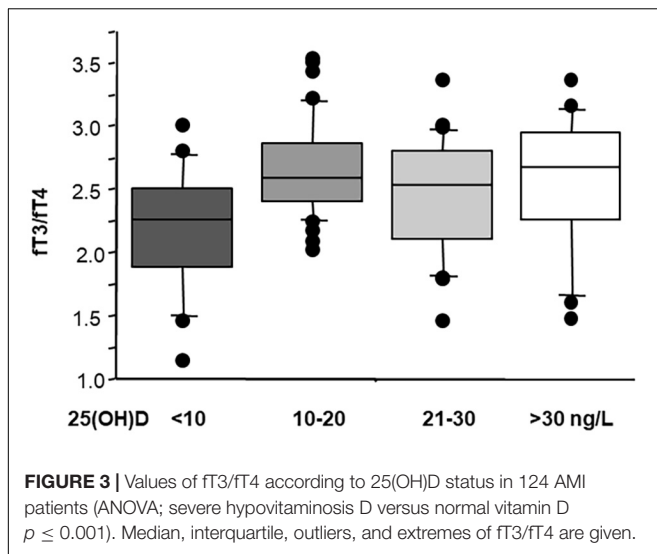
In this context, the case of Low T3 Syndrome (LT3) after AMI is interesting for its clinical significance (Jabbar et al., 2017). LT3 syndrome is characterized by an isolated reduction of blood T3 concentration with normal T4 and TSH levels (Jabbar et al., 2017). This condition interests about 20% of acute MI patients,

and it is associated with more severe clinical manifestations (left ventricular dysfunction, large MI, and inflammatory and stress responses), and adverse prognosis (rate of major cardiac events and a short- and long-term mortality) (Razvi et al., 2018). Changes in blood THs after acute MI may be the result of increased DIO3 activity and reduced DIO1 and DIO2 activities (Olivares et al., 2007; Van den Berghe, 2014). At present, the utility of TH therapy in the management of acute MI is evaluated in early-phase clinical trials for improvement of TH profile, although also looking after possible important adverse effects related to supraphysiological doses as adverse effects in the application of this treatment (Razvi et al., 2018). Thus, in this context, the possibility to use vitamin D supplementation (safe and very rarely toxic even at high doses) instead or in combination with TH treatment in acute MI settings may be of interest. We evidenced that there is a relationship between LT3 syndrome and hypovitaminosis D in acute MI patients (submitted data). In the same population, we observed that patients with low vitamin D (deficient and insufficient groups) showed a trend toward higher TSH levels in comparison to patients who had adequate or optimal levels of vitamin D (1.8 ± 1.8 versus 1.4 ± 1.0), finding particularly evident in those with a severe hypovitaminosis D ($< 10\text{ng/L}$), although without reaching significance values (likely the number of patients enrolled, $n = 120$, needs to be increased) (Table 1). Moreover, patients had higher TSH levels in the Spring-Winter period as opposed to the Autumn-Summer season, according to previous data consistently reporting a significant TSH increase in the colder periods (Table 1; Maes et al., 1997; Das et al., 2018). Higher TSH levels in colder seasons can be due, almost partially, to TSH hypersecretion in response to lower ambient temperature, lower peripheral metabolism and change in diet and physical activity (Danforth et al., 1979; Shinomiya et al., 2014; Louzada et al., 2014). However, we also observed an inverse seasonal trend for 25(OH)D and TSH, as previously reported (Table 1; Barchetta et al., 2015; Das et al., 2018). This fact may suggest that vitamin D may have a role in the modulation of TSH secretion, similarly to its regulatory role on other pituitary hormones (e.g., growth hormone; Esposito et al., 2019).

Notably, patients with a severe hypovitaminosis D [25(OH)D < 10 ng/L] showed lowest fT3/fT4 levels (a TH index, which reflect deiodinase activity and conversion of T4 to T3), suggesting that this category of patients may require more attention and could benefit more from 25(OH)D supplementation (Figure 3). This fact is further confirmed by previous data, showing that stable coronary artery disease prevalence and severity (multivessel disease) was particularly higher in patients with severe hypovitaminosis D (< 10 ng/ml)

TABLE 1 | TSH values according to 25(OH)D status in the overall population and in different seasons.

		<10	10–30	>30 ng/L
TSH (mU/L)	All patients	1.83 ± 1.6	1.78 ± 2.0	1.42 ± 1.0
	mean ± DS			
	Winter-Spring	1.93 ± 1.9	1.92 ± 2.2	1.44 ± 1.1
	Summer-Autumn	1.7 ± 1.2	1.3 ± 0.5	1.3 ± 0.7



(Verdoia et al., 2014, 2021; Nardin et al., 2016), where the effects obtained through restoration of sufficient 25(OH)D levels may be further evaluated in future studies.

Moreover, we also observed that acute MI patients in the group of severe hypovitaminosis D are older than the subjects belonging to the other categories (ANOVA; $p < 0.01$) and more frequently present T2D (43%, ANOVA; $p < 0.01$). Interestingly, patients in the group of 25(OH)D > 30 ng/L do not present T2D, suggesting a negative predictive value for T2D in those with sufficient vitamin D status in this population.

VITAMIN D AND INFECTIOUS AND OTHER IMMUNE-RELATED DISEASES

A relationship between 25-hydroxyvitamin D hypovitaminosis and increased risk of developing different immune-related conditions and infectious diseases has been observed, and recently reviewed (Charoenngam and Holick, 2020). In particular low 25(OH)D levels have been associated to psoriasis, type 1 diabetes, multiple sclerosis, rheumatoid arthritis, tuberculosis, sepsis, respiratory infection, and also COVID-19 (Ponsonby et al., 2005; Megna et al., 2020; Cristelo et al., 2021; Jaimni et al., 2021; Wald et al., 2021; Chetty and Chetty, 2021).

From these observations, many attempts have been made to utilize vitamin D supplementation as a treatment or co-treatment in addition to traditional immunomodulatory drugs. Unfortunately, there are not yet shared protocols of 25(OH)D supplementation in the different conditions, also due to the many variables that take place [e.g., dose, route of administration, dietary interference, genetic individual characteristics, and age, body mass index, season and sunlight exposure, baseline levels of 25(OH)D, patient typology, and supplementation time, and type of outcome measurements]. Thus, available data are heterogeneous,

and as such not definitive and sometimes controversial (Charoenngam and Holick, 2020).

Moreover, for it concerns association between vitamin D and Sars-CoV-2 infection, emerging data indicate that severe vitamin D deficiency resulted more common in COVID-19 patients, playing a significant role in worsening the prognosis of these patients, suggesting vitamin D supplementation as a possible prophylactic and therapy in this setting (Grant et al., 2020; Brito et al., 2021; Campi et al., 2021; Güven and Gültekin, 2021). On this regard, a previous meta-analysis evidenced that vitamin D supplementation resulted safe and protective against acute respiratory tract infection, with patients with severely deficiency experienced the major benefit (Martineau et al., 2017). For COVID-19 patients, a dosage of 50,000 IU of vitamin D3 twice a week for the first week and the dose of 50,000 IU for the second and third week was suggested to reach and maintain levels above 40 ng/ml (Ebadi and Montano-Loza, 2020). Interestingly, a small cohort observational study evidenced that combined oral doses of vitamin D (1000 IU), Mg (150 mg), and vitamin B12 (500 μ g) was associated with a significant reduction in the proportion of COVID patients with clinical worsening (requiring oxygen support, intensive care support, or both) (Tan et al., 2020).

Interestingly, seen the adverse repercussions of Sars-CoV-2 infection on the cardiovascular system and thyroid function, whether the use of supplementation to maintain sufficient vitamin D levels may alleviate these conditions and their complications in COVID-19 patients remains to be better elucidated (Gorini et al., 2020; Kumari et al., 2020; Zhang et al., 2020; Ansari Ramandi et al., 2021).

CONCLUSION

For many years medicine has been developing into separate, specialized, almost independent branches. However, much evidence reveals significant connections between organs, until now considered as single entities, revealing a complex intermingled network with a common list of causes, or contributing factors for “different diseases,” attesting for shared cellular and molecular mechanisms for their etiology and progression. So, we must approach a more holistic view to better understand pathophysiology and improve care of our patients. Certainly, a lot of aspects are not clear. Currently, there is not enough strong evidence to support screening for vitamin D deficiency or vitamin D supplementation in thyroid profile and CV disease setting with the purpose of risk reduction, or improvement of these conditions. Several factors will be still considered in future studies, such as seasonal adjustment of vitamin D levels, and variable populations and definite reference 25(OH)D values for deficiency in extra-skeletal conditions, such as CV disease. Moreover, most studies are based on a single measurement of serum vitamin D levels, which may not be the best indicator of 25(OH)D over time. Nonetheless, even considering the deepening of these aspects, available evidence suggested a role of vitamin D in the relationship between THs

and cardiometabolic disease, providing vitamin D as a potential additional, effective, low-cost, easily available and safe tool to be evaluate in the clinical practice for multi-organ and multi-disease benefits.

METHODS

We have performed a search for articles in PubMed to identify pertinent literature, till 13 August 2021, with the following primary keywords: “COVID-19,” “Sars-CoV-2,”

“vitamin D,” “25(OH)D,” “thyroid,” “cardiovascular disease,” “supplementation,” “thyroid hormones,” with interposition of the Boolean operator “AND.”

AUTHOR CONTRIBUTIONS

CV conceived the manuscript and wrote the original draft. LS wrote the TH/CV part and took care of the graphical figure development. All authors read and approved the final version of the manuscript.

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