Vitamin D and endocrine disorders: routine laboratory diagnostic implications

Giovanna Muscogiuri[1], Harjit Pal Bhattoa[2]

[1] Department of Clinical Medicine and Surgery, Endocrinology Unit, Federico II University, Medical School of Naples, Italy

[2] Department of Laboratory Medicine, Faculty of Medicine, University of Debrecen, Hungary

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Corresponding author:
Giovanna Muscogiuri
Department of Clinical Medicine and Surgery
Endocrinology Unit
Federico II University
Medical School of Naples
Italy
E-mail: Giovanna.muscogiuri@gmail.com

ABSTRACT

The role of vitamin D in calcium-phosphorus metabolism regulation is the most highlighted, nonetheless there is enormous literature on the extra-skeletal effects of vitamin D, and lately new insight into the role of vitamin D in endocrine disease mechanisms has seen light of day. The present narrative review gives an overview of the proposed roles of vitamin D in the etiology of Hashimoto's thyroiditis, Grave's disease, Addison's disease and primary hyperthyroidism. The implications as pertaining to the routine laboratory practice are readily applicable to this patient group as well, and do not pose any additional challenge.

INTRODUCTION

The role of vitamin D in calcium-phosphorus metabolism regulation is the most highlighted, nonetheless there is enormous literature on the extra-skeletal effects of vitamin D [1]. It is known that non-skeletal cells, including those of the endocrine system, too express vitamin D receptor and as such interact with the active form of vitamin D, i.e., 1,25-dihydroxyvitamin D, furthermore, most of these cells express extra-renal forms of 25-hydroxyvitamin D-1α-hydroxylase enzyme and, eventually the active form of vitamin D is known to regulate quite a number of genes, including those implicated in proliferation, differentiation and apoptosis [2-5]. Recently, it has been described that the pathophysiology of autoimmune thyroid disease, adrenal disease and hyperparathyroidism has a Vitamin D component [6-12]. The present review discusses the association between vitamin D status and the aforementioned endocrine conditions and delineates the routine laboratory assessment of vitamin D metabolites.

VITAMIN D AND HASHIMOTO'S THYROIDITIS

Hashimoto's thyroiditis is an autoimmune disease with defective suppressor T-cell function. Thyrocytes in this disease condition express major histocompatibility complex class II (MHC II) surface HLA-DR antigens, as a result of cytokines produced by T helper 1 (Th1) cells, making them prone to immunologic attack as such triggering the autoimmune process. Subsequently the T cell activated B lymphocytes produce autoantibodies reacting with thyroid antigens [9,13,14].

The active form of vitamin D suppresses the autoimmunity in Hashimoto's thyroiditis at a number of stages. Initially it may suppress dendrocyte mediated T lymphocyte activation, may cause blunting of Th1 cell proliferation and its interferone gamma secretion. By the inhibition of cytokine production, it may block MHCII surface HLA-DR expression on thyrocytes. Additionally, B cell proliferation, as a result of activation by T cells, may be seduced and B cell apoptosis may be accelerated by 1,25-hydroxyvitamin D. Hence, active vitamin D may decrease the autoantibody load [8,13,14].

Lately, studies have reported increased risk of Hashimoto's thyroiditis where vitamin D levels may be low, and in conditions where vitamin D functionality may be compromised, as in certain gene polymorphisms of the vitamin D receptor (VDR) and abnormality in vitamin D-binding protein [15,16]. Nonetheless, solid data are necessary to clarify the link between vitamin D status and Hashimoto's thyroiditis.

VITAMIN D AND GRAVE'S DISEASE

In Grave's disease TSH receptor autoantibodies cause hyperthyroidism. Reflected in the increasing interest in the role of vitamin D in susceptibility to autoimmune conditions, potentially this autoimmune disease may also be linked to vitamin D. This may be candidly assumed since it is known that vitamin D suppresses activated T cell proliferation and encourages macrophage phagocytic ability [17,18].

Grave's diseases' etiology has been reported to be associated with VDR and vitamin D binding protein gene polymorphism, presumably by vitamin D function reduction, that may consequently have inhibitory effects on immune regulation [19,20].

These effects appear to be ethnicity specific, Asians with ApaI, BsmI and FokI polymorphisms seem to have a higher susceptibility as compared to their Caucasian counterparts [21]. Additionally, it has also been reported that autoimmune thyroiditis is associated with BsmI and TaqI polymorphism, whereas ApaI and FokI are not [22].

Those with increased ultrasonography measured thyroid volume and early-onset disease

are reported to have low vitamin D levels [23]. Additionally, those in remission were reported to have higher vitamin D levels as compared to their non-remittent counterparts [24]. Although data at present is meager, further studies on the role of vitamin in Grave's disease are worthwhile.

VITAMIN D AND ADDISON'S DISEASE

Addison's disease results from destruction of the adrenal cortex due to an autoimmune process, and may present solitarily or as a polyendocrine syndrome. Although elusive, the etiology of the disease currently suggests that environmental factors along with a genetic component may be responsible for the destruction of the adrenal cortex mediated by CD8 lymphocytic infiltration and autoantibodies against the 21 hydroxylase enzyme [25]. Genetic susceptibility is identified primarily at the HLA locus, but VDR and CYP27B1 genes have also been implicated [26,27].

Given the genetic background it may be assumed that vitamin D is involved in major pathophysiological pathways, as active vitamin D may downregulate CYP21A2 and upregulate CYP17A1 and CYP11A1, as such disrupt steroidogenesis. Additionally, vitamin D also acts on the adrenal tissue along with the immune system in adrenal cell models [28].

Although vitamin D levels comparing controls and Addison's disease patients are not available, the association between vitamin D status and susceptible gene loci may allow one to presume the vitamin's disease modifying role. Nonetheless, there is a need for studies investigating the function and relevance of vitamin D.

VITAMIN D AND PRIMARY HYPERPARATHYROIDISM

The tight regulation of serum ionized calcium level is a result of orchestrated regulation by the parathyroid hormone (PTH), calcitonin and active vitamin D. The biosynthesis of active vitamin D is primarily achieved by the renal CYP27B1, which is stimulated by PTH. Conversely, active vitamin D and ionized calcium downregulate PTH.

The inactive, 25-hydroxyvitamin D is a potent regulator of parathyroid tissue. In contrast to other tissue, parathyroid cells readily take up vitamin D binding protein along with its 25-hydroxyvitamin D, as such guaranteeing better hold of the circulating 25-hydroxyvitamin D.

Additionally, the gland possesses CYP27B1 ensuring 1,25 dihydroxyvitamin D production for paracrine action. This proficient access to both circulating 25-hydroxyvitamin D and 1,25 dihydroxyvitamin D, in addition to its inherent production of 1,25 hydroxyvitamin D induces suppression of PTH secretion and proliferation of parathyroid cells [29].

It is known that sizable parathyroid adenomas have poor feedback by calcium and active vitamin D, as a result in primary hyperthyroidism, 1,25 dihydroxyvitamin D correlate positively with 25 hydroxyvitamin D [30]. Primary hyperthyroidism remains latent, i.e., normocalcemic primary hyperparathyroidism, when circulating vitamin levels are low [31]. Increased 25 hydroxyvitamin D levels and elevated PTH activate renal CYP27B1 accelerating 1,25 dihydroxyvitamin D production in approximation to the 25 hydroxyvitamin D and consequently causing hypercalcemia. This relationship highlights a fundamental aspect of the vitamin D system: its operation under first-order reaction kinetics, namely, the yield of the product (1,25 dihydroxyvitamin D) is proportional to the supply of the substrate (25 hydroxyvitamin D).

As such, the yield of 1,25 dihydroxyvitamin D is proportional to the supply of 25 hydroxyvitamin D and hence qualifying the kinetics of the vitamin D system as a first-order reaction. Consequently, the vitamin D system enzymes modify their function depending on the supply

of 25 hydroxyvitamin D. Depending on severity, primary hyperparathyroidism can disrupt the adaptation, resulting in elevated 1,25 dihydroxyvitamin D and increased intestinal calcium absorption. In primary hyperthyroidism this functional adaptation may be disrupted causing increased 1,25 dihydroxyvitamin D production and as such increased intestinal absorption of calcium. Given the relatively high prevalence of parathyroid adenomas, the hypercalcemia is not a manifestation of overt vitamin D toxicity rather a hypersensitivity to the high dose of vitamin D [32].

In the healthy, increasing 25 hydroxyvitamin D levels are known to decrease serum PTH concentrations. As such, PTH levels may serve as determinants for vitamin D level adequacy. This association does not hold in primary hyperparathyroidism, where the high PTH levels cause unregulated overproduction of 1,25 dihydroxyvitamin D, a potent hypercalcemic hormone. Nonetheless, the role of vitamin D in primary hyperthyroidism needs clarification.

ROUTINE LABORATORY DIAGNOSTIC IMPLICATIONS

Given the implication of vitamin D, as summarized in the above sections, the number of samples sent for measurement of total 25-hydroxyvitamin D to the routine laboratory may increase from patients suspected or diagnosed with the above mentioned common endocrine disorders. Apart from the laboratory tests routinely requested from patients suffering from endocrine conditions, 25-hydroxyvitamin D measurements may well become part of the routine diagnostic and follow-up panel for this patient group.

An additional sampling tube need not be drawn for the procedure, since the primary tube sent for the routine endocrine laboratory tests would suffice for total 25-hydroxyvitamin D measurement as well. Furthermore, no extraordinary preanalytical requirements need to be fulfilled apart from those already expected when drawing samples for routine endocrine testing. Total 25-hydroxyvitamin D measurement methodology has long enjoyed the boons of automatization and test results would ideally be delivered within a short turnaround time.

Lately, the technological advancements in the measurement of 1,25 dihydroxyvitamin D have made the methodology commercially available allowing application to platforms in use at the routine albeit specialized laboratory setting, although the gold-standard 1,25-dihydroxyvitamin D liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay may not be readily available at the basic laboratory level, a recently introduced automated chemiluminescence immunoassay may increase the popularity of this testing [33-36].

Nonetheless, data on 1,25 dihydroxyvitamin D and its implications in various disease contexts, including endocrine disorders, is limited and there will probably be a lapse before mass requests for 1,25 dihydroxyvitamin D measurements overwhelm the routine diagnostic laboratory. Technically, the short half-life of about 4 hours and its minute concentrations in the pmol/L range have limited its utility in a routine setting.

Given the data presented in literature, the 75 nmol/L rather than the 50 nmol/L would plausibly suffice as the desired target value to reap all benefits of vitamin D as implied in its various non-skeletal effects [37].

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