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New light on an old vitamin: The role of the sunshine vitamin D in chronic disease

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During my residency and training as an endocrinologist, I began to get interested in the study of vitamin D. In the past, vitamin D has been considered to be an essential vitamin for bone health but in recent years something has changed. I can affirm that there was a *rediscovery* of vitamin D; it is not just the "*bone vitamin*" but it has been shown to be a hormone with several nonskeletal actions. The increased consensus on the pleiotropic effects of vitamin D and the high prevalence of hypovitaminosis D in the general healthy population have increased the interest in vitamin D among researchers, clinicians, and the lay public. Lack of vitamin D has been involved in the pathogenesis of several acute and chronic illnesses including musculoskeletal disorders [1], type 1 diabetes [2], type 2 diabetes [3], male hypogonadism [4], polycystic ovary syndrome (PCOS) [5], cancer [6], autism [7], dementia [8] and cardiovascular diseases [9]. Of particular interest is the possible involvement of vitamin D in the treatment of these diseases. Humans derive vitamin D from cutaneous synthesis (in the form of cholecalciferol (D3)), diet (in the form of D3), and nutritional supplements (in the form of D3) or ergocalciferol (D2) [10]. Upon exposure to ultraviolet B radiation (UVB), 7-dehydrocholesterol in the skin is converted to pre-vitamin D3, which is immediately converted to vitamin D3 in a heat-dependent process.

After ingestion or synthesis, vitamin D is hydroxylated in the liver to form 25 hydroxyvitamin D (25(OH)D2 or 25(OH)D3, its major circulating form, which has little biological activity. 25(OH)D is converted in the kidney by 25(OH)D-1alpha-hydroxylase (CYP27B1), to its bioactive hormonal metabolite 1,25 dihydroxy-vitamin D (1,25(OH)2D or calcitriol). The primary action of 1,25(OH)2D is through the nuclear vitamin D receptor (VDR), which heterodimerizes with the retinoid X receptor and binds to vitamin D-responsive elements near target genes [10, 11]. The primary action of 1,25(OH)2D is to enhance intestinal calcium absorption and to promote osteoclast function, thereby keeping calcium and phosphorus homeostasis and bone health. However, the discovery that nearly all tissues in the body express the VDR and that several tissues also express CYP27B1, thereby allowing for local production of 1,25(OH)2D with a paracrine effect, has provided important insights into the pleiotropic effects of vitamin D and its potential role in a variety of extra-skeletal tissues [11]. There is no consensus on the 25(OH)D thresholds for defining vitamin D adequacy in order to prevent and/or treat chronic diseases. The only recommendations are related to skeletal outcomes. The guidelines by the Institute of Medicine (IOM) and the Endocrine Society differ on classification of vitamin D status [12, 13]. These differences are explained by the populations targeted by the guidelines and how the evidence was synthesized. Specifically, the IOM guidelines concentrated on the general healthy population and considered only trials, concluding that blood concentrations of 25(OH)D > 20 ng/ml are consistent with favorable skeletal outcomes. In contrast, the Endocrine Society clinical practice guidelines concentrated on people at high risk for vitamin D deficiency and considered both trials and observational (epidemiologic) studies in concluding that blood concentrations of 25(OH)D > 30 ng/ml are desirable for optimal skeletal outcomes without any upper limit that would be concerning for safety. Based on this evidence, this guest issue was created with the aim to gather a selected international panel of independent scientific experts in order to develop a series of evidence-based reviews

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providing the current state of the art on vitamin D status in chronic diseases, identifying the 25(OH)D threshold that might increase the risk of developing diseases and that might be desirable in order to prevent and/or cure them.

With the prevalence of hypovitaminosis D reaching epidemic proportions, the first article in Part 1 of this guest issue is dedicated to this topic. Professor Holick [14] will provide an interesting overview of the epidemiologic data regarding hypovitaminosis D worldwide. Grant and colleagues [15] will review the evidence for vitamin D in reducing incidence of and increasing survival from breast, colorectal, lung, ovarian, pancreatic, and prostate cancer. In fact, the current scientific evidence suggests that vitamin D can exert protective and antitumorigenic activities that would retard cellular transformation, hyperplasia and cancer progression. Cannell [16] will highlight the paramount importance of having sufficient levels of vitamin D during infancy and childhood which are important stages of life for neuropsychological development. Insufficient levels of vitamin D at these stages have been associated with an increased risk of developing autism. Vitamin D is an important immunomodulator and its deficiency could have a role in the pathogenesis of psoriasis. In this regard, Barrea and colleguaes [17] will describe the mechanisms that link these diseases reporting observational and molecular studies. One of the factors that could contribute to hypovitaminosis D has been identified in air pollution that in turn is also responsible for the onset of metabolic diseases such as obesity. Barrea and colleagues will focus on this pathological triad (hypovitaminosis D, obesity, and air pollution) highlighting the common pathological pathways. Savastano and colleguaes [18] will thoroughly address the link between obesity and hypovitaminosis D. In fact, obese people have an increased chance to develop hypovitamonosis D because vitamin D is trapped in adipose tissue due to its lipophilic properties. In turn, hypovitaminosis D has been reported to contribute to *obesity-related* diseases such as insulin resistance. In this regard, hypovitaminosis D seems to be a predisposing factor for development of type 2 diabetes. Grammatiki and colleagues [19] will shed light into the link between vitamin D deficiency and diabetes, explore mechanistic pathways, assess current clinical recommendations and identify areas for future research. Garbossa and Folli [20] will explore the hypothesis that the connection between hypovitaminosis D and glucose derangements could be subclinical inflammation elucidating the pathophysiology of the mechanistic relationship between vitamin D, subinflammation, and insulin resistance, in humans. Insulin resistance is the underlying cause of metabolic syndrome that in turn is a condition characterized by an increased risk of developing cardiovascular diseases. Thus, Gruebler and colleagues [21] will focus on the association of hypovitaminosis D and cardiovascular risk factors through an accurate assessment of the current evidence.

In Part 2 of this guest issue, Wagner and colleagues [22] will focus on pregnancy reporting evidence that support the important role of adequate vitamin D replacement in pregnant women in order to prevent complications during pregnancy, birth and postnatal. Next, Muscogiuri and colleagues [23] will address the role of vitamin D in the pathogenesis of polycystic ovarian syndrome and endometriosis. Sarno and colleagues [24] then will focus on a particular setting of patients that are those who have received kidney transplantation. In fact, hypovitaminosis D seems to be related to several post-transplant complications that can affect both endocrine and metabolic aspects. Altieri and colleagues [25] will illustrate new insights into the pathogenesis of autoimmune diseases, emphasizing the role of vitamin D. Nettore and colleagues [26] will provide a nice overview of observational studies and of the mechanisms that may relate vitamin D to thyroid diseases followed by an excellent review on adrenal gland diseases and vitamin D by Tirabassi and colleagues [27]. Concluding Part 2 of the vitamin D guest issues, Batthoa and colleagues [28] illustrate the last evidence on the association on vitamin D and musculoskeletal health.

Finally, I express my special thanks to Professor Koch who as an *experienced sailor* has helped me navigate in the fascinating seas of the vitamin D research field. I hope that these guest issues will promote the knowledge on vitamin D and represent the basis for future studies on this topic.

Compliance with ethical standards

Conflict of Interest The author declares that there is no conflict of interest related to this work.

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