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ABSTRACT

Rising environmental temperatures induced by climate change cause several physiological responses linked to morbidity and mortality. In this context, heat stress may also contribute to vitamin D deficiency (VDD) through its ability to activate the hypothalamus - hypophyseal axis and cortisol release. VDD may be determined by chronic cortisol exposure, becoming an indirect consequence of an imbalance in glucocorticoid metabolism induced by heat stress in living environment. Several studies suggest the ability of cortisol to increase the catabolism of vitamin D by activating the cytochrome P450 enzymes (CYP), especially CYP24A1 and CYP3A1, and to compete with vitamin D at steroid receptor level leading to potential VDD. This phenomenon could also reinforce the weak influence of non-genetic and genetic determinants of change in vitamin D levels.

Keywords: rising temperatures, heat stress, cortisol, vitamin D, cytochrome P450, vitamin D deficiency

Rising environmental temperatures and heat stress induced by climate change cause several physiological responses linked to morbidity and mortality, especially in vulnerable people such as elderly, people with cardiovascular and other chronic diseases, and very young children. The body temperature reference range is maintained constant by a negative feed - back and feed - forward circuit which re - establishes the homeostatic equilibrium through its effector organs, until the body's thermoregulatory capacity becomes insufficient, resulting in increased core temperature, which combined with ischaemia and oxidative stress after blood redistribution, can cause cell, tissue or organ damage [1-3]. The major body adaptive system involved in the relation between humans and their environment, particularly triggered by heat waves, is the hypothalamus - hypophyseal (HPA) axis, which releases growth hormone, prolactin and especially cortisol in response to environmental stresses [4]. Among these stress hormones, the release of cortisol is correlated with the increase of environmental temperature, becoming significant at temperatures higher than 29°C [5]. In this regard, acute exercise with improper hydration, independently from age, and exposure to noise in heat stress exposure can further enhance the release of human plasma and salivary cortisol [5-7]. Circulating blood levels of this hormone are regulated by food nutrients, suggesting that several factors, including diet and lifestyle, can also influence circulating glucocorticoids levels determined by high temperature living environment [8]. Among all the drivers of human health which are influenced by diet and lifestyle, vitamin D, name used to refer to the animal-derived cholecalciferol, or vitamin D_3, represents a hormone involved in several physiological mechanisms, whose main sources are sunlight and diet. Vitamin D deficiency (VDD) constitutes a shared risk factor of several extra-skeletal pathologies, in addition to rickets and osteomalacia, such as autoimmune disorders, infections, respiratory diseases, cardiovascular disorders, neurodegenerative and neuropsychological diseases and several types of cancers [9-10].

Although an acceptable level of vitamin D is provided either through exposure to sunlight, which is the main source, or through intake from diet, which is supplementary, there is persuasive evidence demonstrating that there are other environmental factors that may interfere in vitamin D metabolism and increase

the risk of VDD [11]. Several studies have shown a positive relationship between environmental factors, such as temperature and solar radiation, and vitamin D levels [12]. However, a more recent study reports that the relationship between average temperature in the previous month and vitamin D levels varies across the seasons. In spring and summer, after reaching certain temperatures, the increasing trend of Vitamin D levels became less marked and in autumn, when the average temperature reached 29 °C in the previous month, vitamin D levels started to decrease, suggesting a potential inverted U-shaped relationship: too high or too low temperatures led to lower vitamin D levels [13]. Therefore, seasonal temperature variations may contribute to VDD through their ability to activate the HPA axis and cortisol release. In particular,VDD may be determined by chronic cortisol exposure, becoming an indirect consequence of an imbalance in glucocorticoid metabolism induced by heat stress in living environment. About this hypothesis, there is increasing evidence of the potential crosstalk between the glucocorticoid and vitamin D metabolic pathways.

The balance between the activity of the cytochrome P450 enzymes (CYP) involved in bioactivation (CYP27A1 and CYP27B1) and degradation (CYP24A1 and CYP3A1) of 25(OH)D and then of 1,25$(OH)_2$D, the active form of vitamin D, is critical for ensuring its appropriate biological effects and tightly controlled *in vivo*. A recent meta-analysis of observational studies on chronic glucocorticoid users reports that the persistent activation of the cortisol pathway can increase the 25(OH)D catabolism by the activation of CYP24A1 [14]. Several studies *in vitro* and *in vivo* animal models support the evidence that the glucocorticoid excess increases the expression and the activity of CYP24A1 involved in vitamin D metabolism [15]. They also showed that the transcriptional control of 1,25(OH)2D on CYP24A1 is glucocorticoid receptor-dependent. In this context, a more recent study reports that chronic glucocorticoid exposure induces preeclampsia by reducing 1,25$(OH)_2$D levels, especially enhancing the expressions of the catabolic enzyme CYP3A1 [16]. Further, the concomitant production of growth hormone and prolactin released by HPA axis could reinforce or counteract the effects of cortisol on vitamin D metabolism. In particular, the growth hormone and prolactin have up- and down-regulating effects on various cytochrome P450 enzymes

in hepatic tissue, respectively [17]. Other studies also highlight that cortisol can contribute to VDD and osteomalacia through its ability to compete with vitamin D at steroid and xenobiotic receptor level [18-20]. By contrast to other stress hormones, the antagonistic effects of cortisol on vitamin D receptor may overcome potential compensatory mechanisms of vitamin D formation leading to potential VDD.

We therefore hypothesize that the cortisol production induced by heat waves in living environment may adversely affect the vitamin D status (Figure 1). This phenomenon could also reinforce the influence of non-genetic and genetic determinants of change in vitamin D levels, such as adiposity, age, sex, specific diseases and genetic polymorphisms at the level of receptors or enzymes involved in the vitamin D metabolism [21-24].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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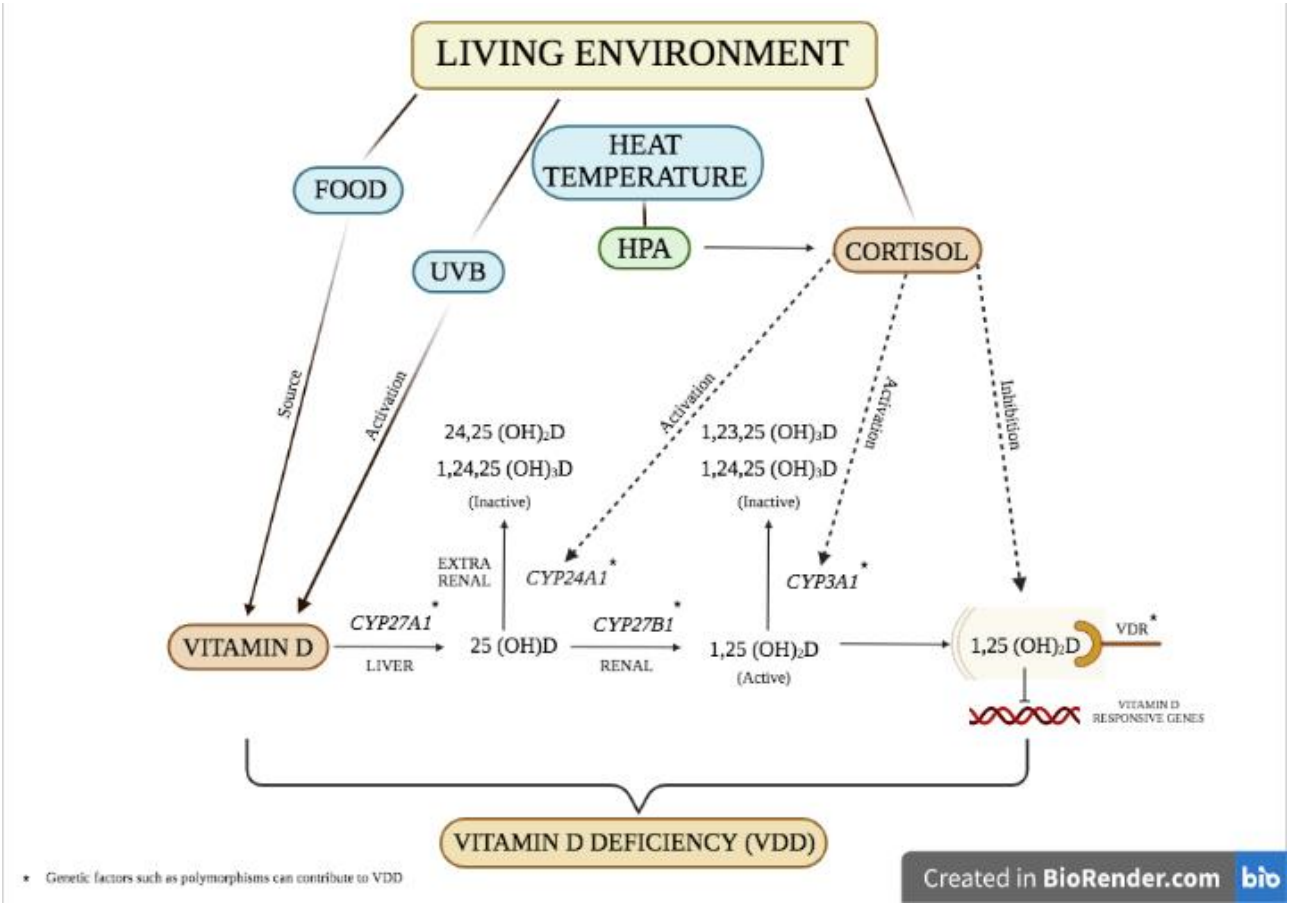

Figure 1. Potential contribution of the heat stress to vitamin D deficiency through its ability to activate the hypothalamus - hypophyseal (HPA) axis and cortisol release.