

Vitamin D; Multi-Potent Hormone

Emad Al-Dujaili*

Reader in Biochemistry and Nutrition, Queen Margaret University, United Kingdom

***Corresponding Author:** Emad Al-Dujaili, Professor of Clinical and Medical Biochemistry, Faculty of Pharmacy, Middle East University, Amman, Jordan.

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Abstract

Since the discovery of vitamin D at the beginning of the 20th century that was later given to children to treat rickets, the implications of vitamin D to our health nowadays are so diverse. It has been shown that vitamin D role is not only in the classical effects of maintaining calcium and phosphate homeostasis in the blood and therefore the formation and maintenance of bones and teeth, but a host of newly substantiated non-classical effects which include the protection against common cancers, cognitive function, cardiovascular disease and its risk factors, immune system function and coordination of innate and adaptive immune responses, multiple sclerosis in humans and others. This mini review is intended to highlight the dangers of the silent hypo vitaminosis D syndrome and the importance of achieving adequate serum vitamin D levels. A crucial issue is to urgently commence optimizing and validating assay methods for vitamin D and its metabolites, as most of these are not reliable or have not been fully validated. Vitamin D and precursors are present only in some foods, and therefore supplements might be necessary especially for people who do not expose themselves sufficiently to sun light or in winter months for northern countries, though few researchers have expressed caution at the present time.

There is now an overwhelming body of evidence for the multiplicity of regulatory and functional roles of vitamin D in the human body exerted through vitamin D receptors (VDR), which are present in many tissues including endothelial cells [1]. The implications of vitamin D to our health are diverse, not only the classical effects of maintaining calcium and phosphate homeostasis in the blood and the formation of bones and teeth, but the newly substantiated non-classical effects which include the protection against common cancers, cardiovascular disease, potent coordination of innate and adaptive immune responses and multiple sclerosis in humans [2]. VDR have a role in the conversion of 25(OH)D [3] to its active form 1,25-di(OH)D, and this has many functions including anti-proliferative effects on vascular smooth muscle, immune and renin-angiotensin-aldosterone systems modulation and stimulating release of inflammatory cytokines [3]. Therefore, the discovery of vitamin D receptors in many tissues has provided new insights into the broad functions of vitamin D and the adverse effects of its deficiency [4]. Several studies suggest that low serum vitamin D levels are associated with hypertension, glucose intolerance, dyslipidaemia, coronary artery calcification and thus, the onset of CVD. Vitamin D is needed for bone growth and remodelling, modulation of cell growth, neuromuscular and immune function and reduction of inflammation. Although the most well-known adverse effect of vitamin D deficiency involves the musculoskeletal system, an increasing body of evidence suggests that low levels of vitamin D may adversely affect the cardiovascular, immune, reproductive systems and others [5,31].

Vitamin D deficiency is highly prevalent worldwide. Low levels of serum vitamin D are present in as many as 30-50% of otherwise healthy adults [5]. Limited synthesis due to inadequate sun exposure, low intake of Vitamin D rich food, pigmented skin, indoor lifestyle and use of sun-screen are the main causes of low serum vitamin D levels, while a poor dietary habits and intake of vitamin D in food or supplement also contributes to the risk of deficiency. Hypovitaminosis D is very common in winter months in the UK; synthesis of vitamin D3 is almost impossible and the majority of the UK population might be vitamin D deficient [6]. Hypovitaminosis D is defined as a serum vitamin D level of < 40 nmol/L [7], though some researchers recommend a level of >75nmol/L to be adequate [8] and 80 to 100nmol/L

as optimal. Experts really don't agree on where the optimal range or even "normal level" is? But a level of 25nmol/L can be considered severely deficient.

In humans, vitamin D known as "sunshine vitamin" is a fat-soluble unique vitamin because it can be synthesised by the body in the skin from sun exposure (UVB light). The sun contributes to 80-90% of vitamin D supply [9], while the diet is a poor source of vitamin D with only 20% of vitamin D supply [8]. Food sources which do contain some vitamin D include oily fish, egg, fortified spreads and breakfast cereals [5]. The term 'vitamin D' is an umbrella term for the two forms of the vitamin: vitamin D₃, which is also known as cholecalciferol and vitamin D₂, which is also known as ergocalciferol. Both of these forms of the vitamin are biologically inactive and so must undergo metabolism to their active form before they can exert their beneficial effects on the body. Epidemiological and clinical studies have proposed an association between low vitamin D status, hypertension and increased CVD events [10], and vitamin D supplementation may potentially reduce BP and improve vascular health through inhibition of renin-angiotensin cascade [3-11]. Cross sectional and observational studies have linked vitamin D deficiency with reduced vascular function and arterial stiffness, a surrogate marker of CVD and cardiovascular health [12-14]. Suboptimal vitamin D levels activate the pro-inflammatory cascade resulting in endothelial dysfunction and increased arterial stiffness and CVD [14].

Recently we have reported at the Society of Endocrinology-BES 2015 conference in Edinburgh, UK that healthy adults supplemented with vitamin D (50 µg/day) had lower blood pressure compared to those given a placebo, as well as having lower levels of the stress hormone, cortisol in their urine. Moreover, A fitness test found that the group taking vitamin D could cycle 6.5 km in 20 minutes, compared to just 5 km at baseline and they also showed lower signs of physical exertion [15]. Our study has received a world-wide interest from athletes and the general public who now have realized the important role vitamin D can play in daily activities and the dangers of its deficiency. Vitamin D deficiency represents a truly silent syndrome linked to various diseases such as insulin resistance, diabetes, rheumatoid arthritis, multiple sclerosis, Parkinson disease, brain dysfunction and a higher risk for certain cancers. Our study and others add to the body of evidence showing the importance of tackling this widespread problem of vitamin D deficiency among the society. Our previous studies suggest that vitamin D can block the action of the enzyme 11-βHSD1, which is needed to activate the "stress hormone" cortisol. High levels of cortisol may raise blood pressure by constricting arteries, narrowing blood vessels and stimulating the kidneys to retain water. As vitamin D may reduce circulating levels of cortisol, it could theoretically improve exercise performance and lower cardiovascular risk factors. Furthermore, an excessive level of the stress hormone cortisol plays a role in CVD including hypertension and atherosclerosis [18]. High urinary cortisol levels are strongly associated with cardiovascular death in subjects with and without pre-existing CVD [19]. Vitamin D deficiency has also been associated with reduced exercise performance in athletes [20]. Researchers have investigated whether vitamin D may benefit exercise performance [21], and reported that in trained athletes, vitamin D intake showed improvement in their performance. The important debate about the optimal daily dietary intake and adequate levels of vitamin D continues about whether athletes do require vitamin D supplements for better performance. Studies suggest a daily intake ranging between 400-2000 IU/ day (10-50 µg/day). If vitamin D does improve muscle function, the implications of this on the performance of athletes who may be vitamin D deficient need to be established. The important issue is whether there is a role for vitamin D supplementation in enhancing performance in such individuals [22-24].

The links between vitamin D level and brain function have strengthened considerably in the past decade, and in a double-blind study [25], vitamin D₃ supplementation was found to stabilize Parkinson disease for a short period in patients with certain genotypes without triggering hypercalcemia [26]. In addition, adequate levels of vitamin D may have a protective effect and lower the risk of developing the debilitating neurological disorder of multiple sclerosis (MS). A study conducted at Maastricht University in the Netherlands and others suggest that for people who already have MS, vitamin D may lessen the frequency and severity of their symptoms. These observations were confirmed by a recent study by Richards group in Canada who reported that a genetically lowered 25(OH)D level is strongly associated with increased susceptibility to MS [27]. Oxidative stress is a major risk factor of CVD and it has been linked with increased rates of atherosclerosis, metabolic syndrome and heart failure, which is triggered by an abnormal production of free radicals [16]. Current studies have suggested a relationship between increased oxidative stress and vitamin D deficiency, thus leading to the question whether vitamin D supplementation has the ability to reduce oxidative stress [17]. The Rotterdam Study have reported that Higher 25(OH)D

concentrations in the elderly were associated with lower prevalence of metabolic syndrome with favourable serum HDL-C, TG and glucose levels [32]. A role for vitamin D in better management of diabetes and dyslipidemia has been suggested by Shenoy, et al. [28] who reported an association between vitamin D, fasting blood glucose, HbA1c and fasting lipid profile in euglycemic Individuals. Two recent studies have reported that decreased vitamin D levels in patients with diabetes had a increased carotid intima-media thickness, and correction of vitamin D deficiency produced a decrease in total cholesterol [33,34]. A study investigated the association of vitamin D status with acute respiratory infections (ARI) in a large cohort of individuals found that levels of 25-OHD were inversely associated with ARI. In a recent paper by Berry, et al. [29] who looked at association of season, lifestyle and health factors with 25(OH)D levels and self-reports of respiratory infections. The effect size was large (about a 10% less risk of infection for every 10nmol/L increase in 25-OHD). Respiratory infections and Meningitis represent failure of the immune system that admits children into the ICU in winter time [30]. In the author opinion, these should be treated not only with conventional antimicrobials, but also with pharmacological doses of vitamin D.

Conclusion

In conclusion, it seems that vitamin D supplementation may be considered as the simplest solution to a wide-ranging health problems. The majority of scientists and clinicians have showed that low blood levels of vitamin D are linked to increased risks of dying prematurely from cardiovascular disease, cancer, and other diseases. However, whether vitamin D supplementation can help people live longer and healthier necessitates more research and clinical trials. The other important issue is to urgently start optimizing and validating assay methods for vitamin D and its metabolites, as most of these are not reliable or have not been fully validated. Only then, blood levels of vitamin D would really be trusted. Vitamin D and precursors are present only in some foods, and therefore supplements are perhaps necessary especially for people who do not expose themselves sufficiently to sun light or in winter months for northern countries. The consensus of how much vitamin D should one takes seems to be about 400IU of vitamin D a day for under 50 years, and 800IU a day for those over 51 years. Only very few researchers have expressed caution at the present time.

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