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Review Article

A Review on Vitamin D as Potential Modulator of Diabetes Mellitus Progression

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Abstract: Vitamin D is a fat-soluble vitamin, and it is involved in a variety of physiological processes such as calcium homeostasis, immune functioning and regulation of cell proliferation. A recent study has also demonstrated its possible involvement in insulin sensitivity, a key biomarker involved in glucose metabolism and T2DM development. The biologically active vitamin D metabolite, 1,25-dihydroxyvitamin D (1,25(OH)2D), acts on VDRs in various tissues including pancreatic beta cells and has an effect on insulin secretion and sensitivity. Given the widespread vitamin D deficiency in T2DM, the association between vitamin D supplementation and insulin sensitivity has been inconsistent across studies. Observational studies generally have found a direct association between them, but randomized controlled trials (RCTs) are more modest. This review critically analyzes mechanisms by which vitamin D may influence metabolic health, such as through inflammation, oxidative stress and calcium homeostasis. It also highlights public health interventions, including food fortification and selective supplementation programs to address vitamin D deficiency and enhance metabolic status.

Keywords: Vitamin D, 1,25(OH)2D, Metabolic Disorders, T2DM**,** Insulin Resistance.

1. INTRODUCTION

Vitamin D is a fat-soluble vitamin, and plays an essential role in various biological processes such as calcium metabolism, immune system function, and cell growth. New studies have proposed a potential implication in anorexigenicity to the modulation of insulin sensitivity, as a central contributor to glucometabolic homeostasis and T2DM pathogenesis. 1,25(OH)2D is the biologically active form of vitamin D that binds to VDR in several tissues including pancreatic beta-cells, stimulating insulin secretion/sensitivity1.

With the increasing prevalence of insulin resistance and related metabolic disorders worldwide, it has been a very hot topic in the public health and clinical fields to investigate potential associations between vitamin D and insulin sensitivity. Curiously, T2DM patients usually suffer from vitamin D deficiency and the insufficiency has been linked with defective insulin secretion combined with exacerbated insulin resistance [3, 4]. Conflicting findings have been reported in the literature with respect to both meta-analysis and clinical trial data regarding whether vitamin D supplementation affects insulin sensitivity, including positive associations in observational studies, but more modest and less consistent associations in randomized controlled trials. The above though raises the heart of the problem: that is, of causation and D-vitamin action on metabolic health (inflammation, oxidative stress but also calcium metabolism), all these factors would in turn impact insulin sensitivity. The potential public health relevance of the relationship between vitamin D and metabolic syndrome is significant. A host of interventions and programs from food fortification to targeted supplementation efforts have been implemented to combat the high levels of deficiency and achieve a better health status in populations at risk 7. Secondary complexity (as the optimal dose and interindividual response) also should be better established before benefit of insulin sensitivity or diabetes prevention can be concluded [9].

1.1 Overview of Vitamin D Functions

1,25(OH)2D, the active metabolite of vitamin D, regulates a variety of biological processes other than its classical role to control calcium and phosphorus homeostasis required for bone health. It promotes the intestinal absorption of this mineral and bone metabolism, as well as it regulates release of calcitonin by parafollicular cells (C cells) of thyroid. In addition, vitamin D has been shown to be involved in immune modulation, and the regulation of cell differentiation and proliferation resulting in antitumor activity 2. Its receptor, the vitamin D receptor (VDR), can be found in almost every tissue and cell in our body, implying that this hormone may have broad effects on numerous physiological processes as well as chronic disease outcomes including cardiovascular health, diabetes and obesity [3].

1.2 Interaction with Vitamin D Receptors

Vitamin D acts through VDRs, which are members of the steroid/thyroid receptor superfamily. The binding of 1,25(OH)2D to VDR results in the formation of a complex that translocates into the cell nucleus and induces actions on retinoid X receptors (RXRs) to regulate genes expression 4.

More than 200 genes are regulated by this pathway, and these genes indirectly influence bone metabolism as well as other cellular processes that include proliferation, adhesion, and immune function [4]. By controlling these pathways, vitamin D also modulates insulin sensitivity and therefore metabolic health, which is considered highly fundamental in glucose homeostasis and regulation of metabolism.

1.3 Effects on Insulin Secretion and Sensitivity

Vitamin D has been shown to affect insulin secretion and sensitivity, key factors in glucose metabolism. VDR is expressed in the pancreatic β-cell and modulates insulin gene expression and secretion6. Of particular interest is the role of vitamin D in enhancing insulin secretion; deficiency has been linked to reduced insulin secretory capacity and susceptibility to type 2 diabetes [6].

Furthermore, vitamin D can enhance insulin sensitivity through its anti-inflammatory and antioxidant actions. Insulin on the other hand, may be influenced by inflammation as both are related to cytokines especially TNFα which is the main player that associates vitamin D deficiency with insulin resistance 2. Through its anti-inflammatory action, vitamin D helps regulate insulin pathways that increase insulin sensitivity and thus prevent metabolic diseases.

1.4 Calcium Balance and Relationship with Insulin

Calcium is important for the function of pancreatic beta cells and insulin secretion. Vitamin D has a role in keeping cal cium balance by its action on parathyroid hormone (PTH) and also synthesis of calcium binding proteins for insulin secretion [8]. The effect of calcium intake on insulin sensitivity provides additional support for the role of vitamin D in this metabolic pathway. Vitamin D deficiency causes decreased levels of calcium resulting in decreasing insulin secretion and action leading to the development of diseases such as insulin resistance, type 2 diabetes [2]. Recent years have seen increasing focus on application of vitamin D in insulin resistance mechanism, which can be explained by the available Chinese clinical studies and other studies. Vitamin D, classically recognized for its role in bone health, participates in a wide range of metabolic routes including glucose and insulin physiology. It is known from studies that T2DM patients are more likely to be deficient in vitamin D and this raises the question whether supplementing vitamin D could improve insulin sensitivity and control of glucose 1.

1.5 Meta-Analyses and Systematic Reviews

Several meta-analyses have been carried out on this topic to pool evidence on the association between insulin sensitivity and vitamin D levels. For example, a meta-analysis concluded that majority of the observational studies were consistent with an association between higher vitamin D levels and better insulin sensitivity. RCTs were more variable and only some reported significant differences from vitamin D supplementation. A meta-overview of 74 meta-analyses showed that optimistic I-II and conservative III-IV associations were found in observational studies and RCTs, respectively. This discrepancy illustrates the problems of establishing causation rather than association in a clinical setting, and underscores that larger, adequately powered studies will be needed to determine how vitamin D might affect insulin sensitivity 3.

1.6 Vitamin D Supplementation and Administration

Vitamin D supplementation is widely recommended as a first-line approach for vitamin D deficiency, particularly in target populations. Optimal supplementation depends on multiple factors that should be considered including the dose, species of probiotic, and duration. Existing evidence indicates that doses closer to international recommendations are more likely to be effective, since previous research with low dosing continues to provide inconclusive evidence about the effect of vitamin D on health outcomes related to insulin sensitivity and statewide metabolic status [9-3]. Moreover, RCTs have frequently been markedly undersized which reduces the power to detect large effects [9]. Consequently, a large well-executed RCT is needed to determine the optimal supplementation criteria.

1.7 Dietary Sources and Bio-Fortification

In addition to supplementation, dietary vitamin D sources are also important in the management of deficiency. Dietary forms of food (e.g., fatty fish, fortified dairy products, UV-treated mushrooms) as food sources can supplement intakes [3]. The development and implementation of bio-fortification methods, including fortification of animal feed with vitamin D or treatment of foods using UV radiation, are particularly appealing as strategies to increase population-level intake of vitamin D [3]. This has been successful in some studies but with varying levels of evidence and so further research is required on the most effective methods to bio-fortify populations for improvement in vitamin D status particularly within multi-cultural populations.

1.8 Assessment and Monitoring of Vitamin D Status

The diagnosis of vitamin D deficiency is based on a blood test, which is best performed to measure the circulating 25-hydroxyvitamin D concentration. Current optimal range is 30–100 ng/mL, while less than 30 ng/mL is inadequate [2]. These high-risk groups - women of childbearing age, the obese - already have a lower vitamin D baseline levels so we may need to be checking them regularly 2. However, accessibility and cost of testing for vitamin D are challenged with the feasibility of mass screening and monitoring.

1.9 Correcting Deficiencies in Special Populations

Of note, interventions in special populations who have increased rates of vitamin D deficiency, such as women of childbearing age and certain ethnic groups may be particularly important. For instance, it has well been studied that 80% of women in the Middle East during reproductive period suffered from vitamin D deficiency and this is obviously a need for robust public health policy to prevent such situation [3]. Recommended interventions may be of personalized supplementation schedules and if education intervention to improve the consumption of fortified foods.

1.10 Epidemiology of Vitamin D Deficiency in Public Health

Recent investigations have shown the positive results of these interventions for improving vitamin D status in diverse populations, including all-year round sunlight exposed population types. Aside from traditional fortification, bio-fortification (a form of food based approach in which the nutritional value of food is increased through agricultural approaches) has also been demonstrated to be a promising approach. This approach provides the natural enrichment of food with vitamin D and is therefore a sustainable way to help meet dietary needs in at-risk populations [11]. New bio-fortification techniques, including vitamin D fortification of eggs and milk through increase in their vitamin D2 content via animal feed or by UV exposure for mushroom are being evaluated and have potential for better consumer acceptability and compliance [12]. Targeted Supplement Programs Supplementation Interventions In addition to food fortification, targeted supplementation of at-risk populations should also be an important public health policy. Certain populations such as pregnant women, children or people with low sun exposure levels generally need additional vitamin D to prevent deficiency risks. Intervention programmes implemented at clinics, schools and communities to deliver supplements of vitamin D have been found effective in raising the mean serum 25(OH)D considerably among the group at risk [1]. Such interventions are of particular significance given the evidence for an association between vitamin D insufficiency and impaired insulin sensitivity, as well as with metabolic syndrome. By managing the vitamin D status of at-risk people, public health can prevent associated burden of type 2 diabetes and other metabolic diseases, and by extension population health [9].

2. CONCLUSION

Vitamin D insufficiency is a significant public health issue with potential implications for insulin sensitivity and glucose control. Although certain prospective studies have suggested that high serum vitamin D is predictive of improved insulin sensitivity, the results from randomized trials are inconclusive and further investigation is required to clarify causality and intervention. Vitamin D high-risk public supplementation and food fortification are needed to reduce the burden of vitamin D deficiency. Future studies also need to be based upon large, well-designed RCTs to confirm efficacy for vitamin D supplementation in enhancing insulin sensitivity and decreasing susceptibility to metabolic diseases (e.g., T2DM). Decentralization of these comprehensive approaches, as has been done by the Osteoporosis Vitamin D Standardization Program [32], is required for ensuring appropriate testing and interpretation, ultimately guiding vitamin D treatment will simply lead to better health.

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