Editorial Commentary



# Does vitamin D supplementation reduce type 2 diabetes risk?

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The morbidity and mortality rates of diabetes have been ever increasing year-on-year basis with approximately 400-million diabetes people; therefore, it represents a pressing issue of public health threat with huge socioeconomic impact worldwide that needs to be dealt with immediately. In fact, diabetes has become a global epidemic associated with the major cause of hospitalization and death among the aging population, where type 2 diabetes mellitus (T2DM) or, predominantly, obesity-associated T2DM accounts for >90% of human diabetes in clinical setting (1). Given that the current therapeutic modalities of T2DM are suboptimal with side effects, we should resort to some plain preventative approaches, such as physical exercise and lifestyle change as well as the use of dietary supplements and food additives, or nutraceuticals (2). Of particular interest in this context is the potential benefit of vitamin D supplementation to reduce hepatic insulin resistance and pancreatic islet dysfunctions, thus opposing the progression and development of obesity-associated metabolic diseases, such as T2DM and non-alcoholic fatty liver disease (NAFLD) (3). In confirmed, leveraging the advantage of vitamin D/analogue supplements may provide a scientific basis for the cost-effective approach to lowering or preventing T2DM risk and its related complications and sequelae.

In term of classical biological functions, vitamin D is a primary regulator of calcium and bone homeostasis, and thus its deficiency results in hypocalcemia and secondary hyperparathyroidism as well as rickets and osteomalacia seen in children and adults, respectively (4). In term of non-classical functions, vitamin D binds with its receptors (VDRs), via the interaction of vitamin D-VDR signaling, to exhibit its novel and myriad physiological roles beyond bone health. In this regard, VDRs or vitamin D-activating hydroxylases are found to be widely distributed and locally expressed in various tissues and organs of the immune, cardiovascular, reproductive and nervous systems (5). Defects in the regulation of vitamin D-VDR signaling axis are thus of clinical relevance to health and diseases, particularly in the context of obesity-related T2DM and NAFLD (3). Given that vitamin D has pleiotropic effects and vitamin D deficiency (hypovitaminosis D) are common worldwide, hypovitaminosis D is believed to be associated with, and predictive of, T2DM or, at least, an independent predictor of insulin resistance as observed in Chinese peoples (6). Mounting evidence from observational studies, meta-analyses, randomized control trials, and etc. have reported an inverse relationship between plasma level of 25-hydroxyvitamin D and T2DM risk; these clinical data might point to high concentration of 25-hydroxyvitamin D being able to prevent T2DM and/or transition of prediabetes to overt diabetes (7-13). Notwithstanding the existence of these findings, whether vitamin D supplementation serves as a potential clinical approach to lowering insulin resistance, improving glycemic indices, and delaying the onset of T2DM remains ambiguous and even controversial.

In a study published in August 2019 in *New England Journal of Medicine*, Pittas *et al.* attempted to further look into this issue of vitamin D supplementation and T2DM prevention using a multicenter, randomized and placebo-controlled trial on a total of 2,423 participants with

1,211 assigned to the vitamin D group and 1,212 to the placebo group (14). The authors conclude that, among persons at high risk for T2DM not selected for vitamin D insufficiency, vitamin $D_3$ supplementation at a dose of 4,000 IU per day did not result in a significantly lower risk of diabetes than placebo (14). In line with the conflicting results from previously performed clinical studies, the work of Pittas *et al.* further underscores the controversy and ambiguity on the relationship of hypovitaminosis D and T2DM risk, as seen in human species. Despite these negative findings, there are still limitation and weakness that commonly exist in the design and conduction of the clinical studies; they include the doses and forms of vitamin D/analogues used, duration of intervention and study populations, and geographical origins as well as nutritional, environmental, genetic factors, and so on involved. While the causality of vitamin D and T2DM status has yet to be established in humans, the protective effects and potential mechanism(s) of vitamin D against insulin resistance, islet dysfunction, hyperglycemia and T2DM in animal species appears to be relatively demonstrated (3,15).

In animal studies, the direct role of hormonal vitamin D (calcitriol) was previously reported to enhance glucose stimulated insulin secretion from mouse isolated islets under high-glucose condition, as demonstrated by an animal model of VDR-knockout mice (16). In addition, calcitriol at above-physiological serum concentration was also shown to reduce hepatic triglyceride accumulation and glucose output, at least in part through activation of $Ca^{2+}$/CaMKKβ/AMPK signalling pathways under insulin-resistant condition (17). These data appear to point to the direct protective effects of vitamin D against islet dysfunction and hepatic insulin resistance in T2DM (3). On the other hand, it was previously reported that vitamin D was a negative endocrine regulator of the renin-angiotensin system (RAS) with clinical relevance in cardiometabolic diseases (18). Interestingly, combined treatment with paricalcitol, an analogue of vitamin D and losartan, an antagonist of angiotensin II type 1 receptor, could increase the efficacy of losartan blockade in a mouse model of T2DM (19). In addition, calcitriol was found to reduce or prevent the RAS overactivity dose-dependently (16). Moreover, pharmacological treatment with aliskiren, a renin inhibitor, was demonstrated to be protective against hypovitaminosis D-induced RAS overactivity, islet dysfunction and insulin resistance, as well as improving glucose intolerance in mice (20). All these data suggest that vitamin D may directly or directly prevent/correct high-glucose activation, and that hypovitaminosis D-induced increase in RAS activity may be suppressed by RAS blockade, as evidenced at least by experimental animal studies. If true, avoidance of vitamin D deficiency and/or RAS blockade may reduce and prevent T2DM risk. Until then, vitamin D supplementation should not be considered a clinical measure for the prevention of T2DM based on current inconsistent and conflicting clinical studies.

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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