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Vitamin D and Diabetes: Association vs. Causation?

Vitamin D deficiency was first described by Daniel Whistler, a British physician, in 1645 and Sniadecki in 1822 identified the relationship between lack of sunlight exposure and the development of vitamin D deficiency in children resulting in rickets [1, 2]. This nutritional factor was termed vitamin D by McCollum [3]. Adolf Windaus in 1928 received the Nobel Prize for the discovery of the structure of vitamin D and 7-dehydrocholesterol and other sterols [4]. The major forms of vitamin D are vitamin D3 and vitamin D2. Vitamin D3 or cholecalciferol is of animal origin whereas vitamin D2 or ergocalciferol is of plant origin. They differ only in their side chain structure and both undergo the same metabolic pathway and have similar physiological actions.

During exposure to sunlight, 7-dehydrocholesterol in the skin absorbs ultraviolet B radiation to form pre-vitamin D3, which is subsequently metabolized to the active form of vitamin D by hydroxylation in the liver (to 25-hydroxy vitamin D, 25(OH)D3) and then in the kidney (1α,25-dihydroxy vitamin D). The average plasma life of 25(OH)D is 3 weeks, and the serum level of 25(OH)D is used to access the body storage status of vitamin D. The classical action of vitamin D is in maintaining bone health by regulating calcium and phosphate homeostasis. Major extra skeletal actions of vitamin D include oxidative stress reduction, anti-inflammatory, and immunoregulatory action, neuroprotection, anti-cancer action, and protection against cardiovascular diseases and diabetes.

Diabetes is a metabolic disorder with chronic hyperglycemia and it is a major risk factor for cardiovascular diseases (CVD). Numerous studies have shown the association between vitamin D deficiency and diabetes; lower levels of vitamin D in people with type 1 as well as type 2 diabetes [5, 6]. Moreover, few, not all, studies suggested an increased risk of diabetes in people with vitamin D deficiency [7].

Many mechanisms have been proposed such as the presence of vitamin D receptors in pancreatic beta cells, which promotes insulin secretion as well as anti-inflammatory actions of vitamin D in pancreatic beta cells, and this is beyond the scope of the discussion for this Editorial.

Most studies suggesting a link between vitamin D deficiency and diabetes or the risk of diabetes are epidemiological or cross-sectional. This type of studies only provides association but not casualty. To prove that vitamin D deficiency is causing diabetes, we need randomized controlled trials. The largest clinical trial, VITamin D and OmegA-3 TriaL (VITAL), was primarily designed to evaluate the effect of vitamin D supplements in the prevention of CVD and cancer [8]. The

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largest trial so far has not shown any benefits of vitamin D supplements in reducing the risk of CVD, cancer, or fracture. This has raised many questions and concerns about the overuse of vitamin D supplements in clinical practice without evidence-based benefits of vitamin D [9]. However, the VITAL study did not address the effect of vitamin D supplements on diabetes risk. A large randomized controlled trial with vitamin D supplements in the Japanese population did not reduce the incidence of diabetes compared to placebo [10]. It remains to be establish whether vitamin D supplements would be helpful in reducing the risk of diabetes or effective in improving glycemic control and prevention of complications.

In this issue, Ehsan Aliniagerdroudbari et al. from Tehran, Iran reported a higher prevalence of vitamin D deficiency in people with type 2 diabetes (vitamin D deficiency was reported in 48%, insufficiency in 21.5%, and sufficiency in 30.5%) and significant direct association between vitamin D and HbA1c levels [11]. The geographical location and air pollution in Tehran may likely be associated with a high prevalence of vitamin D deficiency in this population. However, this study has limitations. The major limitations of this study are: small sample size, lack of sample size determination based on pre-specified outcomes, cross-sectional and single center design. Therefore, this study provides incremental evidence of the existing literature that vitamin D deficiency is common in people with type 2 diabetes. However, cross-sectional studies cannot provide causation. Large randomized controlled trials with pre-specified diabetes-related outcomes (akin to VITAL study for CVD and cancer outcomes) are needed to answer many questions such as whether we should measure vitamin D levels in people with diabetes, when to treat, and what dose of vitamin D and how long treatment is needed to achieve desirable outcomes?

Conflict of interest

None declared.

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