EDITORIAL

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Is vitamin D supplementation really effective in patients with type 2 diabetes?

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Vitamin D deficiency is very common in children and adults. More than 50% of Koreans have vitamin D insufficiency. Because vitamin D plays a major role in calcium absorption and bone metabolism, vitamin D deficiency in adults can cause osteopenia, osteoporosis, muscle weakness, and an increased risk of fracture. Furthermore, vitamin D receptors are distributed in most tissues and cells in the body. Several studies suggest that vitamin D deficiency is associated with diabetes and cardiovascular disease.

The prevalence of vitamin D deficiency is higher in type 2 diabetes patients than in nondiabetes patients [1]. Serum 25-hydroxy vitamin D [25(OH)D] concentration, an indicator of vitamin D status, is positively correlated with insulin sensitivity. Also, vitamin D deficiency was associated with increased insulin resistance, low insulin levels, β-cell dysfunction, and metabolic syndrome [2]. The exact mechanism is not known. Vitamin D receptors are present in pancreatic islet cells and insulin secretory capacity was impaired in mice lacking a functional vitamin D receptor [3]. Another possible mechanism is the inverse association between tumor necrosis factor-α and 25(OH)D and its promotion of insulin resistance [2]. Insulin resistance is also closely associated with the prevalence of diabetes, hypertension, arterial stiffness, and cardiovascular disease.

In experimental studies, vitamin D deficiency was associated with incident cardiovascular disease [4,5]. The mechanism of the association between vitamin D and cardiovascular disease has not been established. Vitamin D deficiency causes secondary hyperparathyroidism. Parathyroid hormone (PTH) promotes myocyte hypertrophy and vascular remodeling and stimulates systemic and vascular inflammation [4]. Also, vitamin D regulates the renin-angiotensin axis by directly suppressing renin gene expression [5]. Vitamin D receptors are present in vascular smooth muscle cells and endothelial cells. They have the ability to convert circulating 25(OH)D into 1,25(OH)D. Then, vitamin D affects smooth muscle cell proliferation, inflammation, and thrombosis [4].

Vitamin D supplementation is effective at elevating the 25(OH)D concentration. However, is it really effective at improving diabetes and cardiovascular disease?

Short- and long-term studies of glucose control and insulin resistance after vitamin D supplementation in type 2 diabetes patients have reported various results. In one study, 100 patients with type 2 diabetes showed significant improvements in serum fasting blood glucose, insulin, and homeostatic model assessment of insulin resistance after 8 weeks of treatment with vitamin D (50,000 IU/

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week) [6]. Another study suggested that the combined daily intake of 1,200 mg of calcium and 800 IU of vitamin D reduced the risk of type 2 diabetes by 33% compared with a daily intake of less than 600 mg of calcium and less than 400 IU of vitamin D [7]. However, several interventional human studies showed that vitamin D supplementation did not improve glucose control and insulin resistance in type 2 diabetes patients [8]. It is difficult to define the effect of vitamin D supplementation in patients with type 2 diabetes because the clinical characteristics of the patients and the dose and duration of calcium-vitamin D supplementation differed between studies.

Several studies investigated the impact of vitamin D supplementation on cardiovascular risk factors. A single dose of 100,000 IU of vitamin D2 improved flow-mediated vasodilatation of the brachial artery by 2.3% in patients with type 2 diabetes [9]. However, in another study, 12 weeks of vitamin D supplementation (5,000 IU/day, n = 50) did not significantly affect vascular function [10]. The cardiovascular effect of vitamin D supplementation in patients with type 2 diabetes is not clear.

In this issue of *The Korean Journal of Internal Medicine*, Ryu et al. [11] investigated the role of vitamin D supplementation in cardiovascular disease risk, including metabolic parameters, insulin resistance, and arterial stiffness in type 2 diabetes. Patients were divided into a vitamin D group (cholecalciferol [2,000 IU/day] + calcium [200 mg/day], n = 40) and a placebo group (calcium 200 [mg/day], n = 41). There were no differences between the groups in the changes in insulin resistance and arterial stiffness after 24 weeks of intervention.

Several cross-sectional, epidemiological studies have shown associations between vitamin D deficiency and increased risks of many chronic illnesses, including cancer, autoimmune disease, infectious disease, cardiovascular disease, diabetes, metabolic syndrome, and depression [7]. However, apart from reducing the risk of falls, vitamin D supplementation did not significantly improve extraskeletal health. In this study, patients with vitamin D deficiency and type 2 diabetes were given sufficient vitamin D supplementation. However, there was no improvement in glucose control, insulin resistance, or arterial stiffness (a surrogate marker of cardiovascular disease risk). The exact cause is unknown, but vitamin D deficiency may not play a major role in the pathogenesis of diabetes.

The strength of this study is that it was a well-designed interventional study of vitamin D in Korean patients with type 2 diabetes. Moreover, it evaluated both insulin resistance and arterial stiffness. However, the sample was small and the results might not accurately reflect the effects of vitamin D because it was coadministered with calcium. In addition, the nonsignificant changes in PTH and C-reactive protein (an inflammatory marker) may have affected the results. Finally, the study duration might have been too short to improve cardiovascular risk factors.

It is difficult to define the effect of vitamin D supplementation in patients with type 2 diabetes. Also, observational studies are limited in their ability to prove a causal relationship. However, as the effect of vitamin D treatment on the progression of diabetes is unclear, its use to treat and prevent diabetes is not appropriate. To date, the only proven effective use of vitamin D treatment is the prevention of osteoporosis and falls. In the future, a high-quality large prospective study is needed to fully determine the effect of vitamin D supplementation in patients with type 2 diabetes.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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