Effect of vitamin D supplementation on pancreatic β-cell destruction and type 1 diabetes

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Type 1 diabetes (T1D) is an organ-specific autoimmune disease with loss of pancreatic β-cells, characterized by reduced insulin levels and increased blood glucose.[1] The incidence of T1D is increasing by approximately 2% to 5% worldwide every year and becoming a global health problem.[2] Vitamin D (VD) deficiency was reported to be a risk factor in the development of T1D.[3] Recent studies showed that supplementation of VD alleviated disease symptoms in T1D patients. However, a few randomized controled trials (RCTs) demonstrated the clinical effect of VD treatment with inconsistent findings. This article aimed to evaluate the effect of VD supplementation in T1D, which is helpful to develop an adjuvant therapy for T1D.

Effects of vitamin D on pancreatic β-cells destruction

The main cause of T1D is a decline in insulin secretion by the pancreatic β-cells. *In vitro* studies demonstrated that 10 nmol/L $1,25(OH)_2D_3$, an active form of VD, increased glucose-stimulated insulin secretion (GSIS) in INS-1E cells by changing the genes involved in β-cell function and viability expression.[4] *In vivo*, vitamin D injection (20,000 IU/kg) improved hyperglycaemia and hypoinsulinemia in diabetic rats, as well as decreasing inflammation by inhibiting nuclear factor-kappa B (NF-κB) activity.[5] Additionally, He *et al*[6] firstly revealed that $1,25(OH)_2D_3$ induced autophagy and increased insulin secretion to protect from oxidative damage in streptozotocin (STZ)-induced T1D mouse model. However, Jeddi *et al*[7] showed that pretreatment of rat islets with $1,25(OH)_2D_3$ (1 nmol/L and 10 nmol/L) increased insulin secretion with glucose (16.7 mmol/L) stimulation, but co-incubation with $1,25(OH)_2D_3$ (1 nmol/L and 10 mol/L) decreased insulin secretion with glucose (16.7 mmol/L) stimulation. The discrepancy perhaps is associated with the dosage of $1,25(OH)_2D_3$ and duration of preincubation.

T1D is an immune-mediated loss of islet cell. $1,25(OH)_2D_3$ protected β-cell against apoptosis by directly decreasing the expression of proinflammatory cytokines thereby inhibiting T1D development.[8] Further, $1,25(OH)_2D_3$ increased antiapoptotic protein A20 expression to block NF-κB activation, which decreased nitric oxide (NO) generation to protect β-cell.[9] Accordingly, Wolden-Kirk *et al*[10] demonstrated a direct protective effect of $1,25(OH)_2D_3$ against inflammation-induced β-cell dysfunction in human and murine islets, especially with alterations in chemokine production by the islets. In addition, the study in our lab revealed $1,25(OH)_2D_3$ protected MIN6 cells from oxidative damage by inhibiting endoplasmic reticulum (ER) stress.[11]

Vitamin D deficiency and T1D

Given that the aforementioned effects of vitamin D against β-cell dysfunction, epidemiologic data have assessed the 25-hydroxycholecalciferol ($25\text{-}OHD_3$) level in T1D patients over the last years. Three meta-analysis demonstrated that serum $25\text{-}OHD_3$ is significantly lower in T1D patients than in healthy controls in 2015 and 2016.[12-14] In the past 3 years, from 96 Korean children with T1D and 156 healthy controls, the mean serum $25\text{-}OHD_3$ levels (19.8 ± 7.2 μg/L) and $1,25(OH)_2D_3$ (32.7 ± 13.0 ng/L) in T1D children were significantly lower than those in healthy individuals (25.1 ± 8.9 μg/L, $P < 0.001$ and 39.6 ± 17.2 ng/L, $P < 0.01$, respectively), indicating VD deficiency prevalence was higher in T1D children than in

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controls.[15] Very similar results were conducted in a large cohort study; Bae *et al*[16] reported the mean serum levels of 25-OHD_3 was considerably lower (21.6 ± 8.5 μg/L *vs.* 28.0 ± 12.0 μg/L, $P < 0.001$) and VD deficiency was more prevalent in T1D than in healthy controls (48% *vs.* 26%, $P < 0.001$). All these results showed VD deficiency was highly prevalent in T1D patients. However, a cross-sectional study including 296 T1D patients and 151 controls showed serum 25-OHD_3 levels were similar between patients and controls (22.9 ± 17.4 μg/L *vs.* 24.5 ± 19.3 μg/L, $P = 0.382$).[17] This discrepancy maybe resulted from the bias of studies on the geographical distribution, age difference and genetic background.

Vitamin D supplementation in T1D

Since VD deficiency is very common in T1D patients, its supplementation may have a beneficial effect in T1D. Recently, a retrospective study demonstrated that treatment of vitamin D_3 (VD_3) improved the glycaemic control, for the mean hemoglobin A1c (HbA1c) was 73.5 ± 14.9 mmol/mol and 65 ± 11.2 mmol/mol ($P < 0.001$) before and after VD_3 administration for 3 months.[18] Very similarly, Panjiyar *et al*[19] demonstrated that T1D patients with VD_3 supplementation lowered HbA1c, fasting blood glucose (FBG) and mean blood glucose (MBG) level. Furthermore, a current prospective cohort study including 30 VD-deficient T1D showed that VD_3 had a significant lowering effect on HbA1c ($8.93\% \pm 1.85\%$ *vs.* $8.72\% \pm 1.45\%$, $P = 0.04$) after 4 months of VD_3 therapy.[20] However, a double-blinded RCT showed that VD_3 in addition to insulin therapy (intervention group) for 6 months did not result in any significant difference in mean HbA1c and insulin requirements compared to insulin therapy alone (control group) in T1D children.[21] Also, in UK, an interventional study indicated that oral VD_3 treatment showed no effect on glycemic control in children with T1D.[22] There is paucity of data to support the widespread use of VD_3 supplementation in T1D patients. Interestingly, a systematic review of seven RCTs showed supplementation with 1α-OHD_3 and VD_3 had significant positive effects on daily insulin dose (DID), fasting C peptide (FCP), stimulated C-peptide (SCP), and HbA1c, whereas supplementation with $1,25(OH)_2D_3$ had no effect.[23] Based on the above data, the inconsistent results [Supplementary Table 1, http://links.lww.com/CM9/A393[18-22,24]] could be due to the dosage, type, duration of vitamin D supplementation, genetic differences and sample sizes.

Future perspectives

In summary, vitamin D deficiency has been confirmed to be closely related to pancreatic β-cell destruction and T1D. The prevalence of T1D is increasing worldwide and currently, exogenous insulin injection is a major treatment for T1D patients with certain side effects, such as chronic macrovascular and microvascular complications. Therefore, developing a novel therapy to maintain endogenous insulin production would be beneficial in controlling glucose level and preventing complications of diabetes. However, the effects of vitamin D on prevention or treatment of T1D remains controversial. Thus, more long-time and large-scale studies are required to evaluate the role of vitamin D supplementation in T1D. Further studies are needed to establish the duration of therapy, the optimal dose, the appropriate form of vitamin D [VD_3, alfacalcidol (1α-OHD_3), 25-OHD_3, $1,25(OH)_2D_3$] or its analogs to elucidate the conclusion. In the future, we hope vitamin D will be used as an adjuvant therapy to improve the quality of life of T1D patients.

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Conflicts of interest

None.

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