Vitamin D and diabetes; a review

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Despite advanced therapeutic and primary prevention strategies, diabetes mellitus remains a significant global health care problem. Substantial morbidity and mortality associated with the disease, emphasize the importance of primary prevention. In Sri Lanka the prevalence of diabetes among male is 14.2% and 13.5% among females and these figures are expected to increase over the next few decades (1).

Vitamin D and its active metabolite 1, 25 OH_2 cholecarciferol are widely known for their role in calcium homeostasis and bone metabolism. Recently, there has been a much evolving enthusiasm on the extra skeletal benefits of vitamin D. The basis for this appears to be related to the findings in several observational studies which reveal a close association between vitamin D and the development of autoimmune diseases, malignancies and metabolic abnormalities abnormalities such as type 2 diabetes (2).

The exact mechanism of vitamin D deficiency causing diabetes remains largely unknown. Vitamin D has a beneficial effect on insulin action either directly or indirectly by improving insulin exocytosis via activating calcium depending endopeptidases (3). It has been shown that type 1 diabetes is associated with an imbalance of pro anti-inflammatory cytokines and vitamin D acts as a potent immune suppressor and down regulator of transcription of proinflammatory cytokine genes, reducing the risk of type 1 diabetes (3).

This paper reviews the association of vitamin D with regard to the incidence, morbidity and mortality of diabetes.

Incidence

Several cross-sectional and cohort studies and randomized controlled trials have examined the association between vitamin D and the incidence of type 2 diabetes. A population based cross-sectional study reported a significant inverse association between serum 25 (OH) D3 and the risk of developing diabetes. (OR 0.25, 95% CI 0.11 - 0.60) for non-Hispanic whites and OR 0.17, 95% CI 0.08 - 0.37 for Mexican Americans (4).

Knekt *et al.*,observed that men with highest vitamin D quartile had a 82% lower risk of developing type 2 diabetes compared to men in the lowest vitamin D quartile. No significance association, however, was found among women (5). Nurses' Health Study by Pittas *et al*., showed that higher levels of plasma 25-OHD were associated with a lower risk for type 2 diabetes in women. (The relative OR between highest and lowest vitamin D quartiles was 0.52, 95% CI 0.33 - 0.83) (6).

Few studies such as the Nurses Health Study (7), the Women's Health Study (8) and the Japanese cohort study (9) have assessed the relationship between the dietary intake of vitamin D and the risk of developing diabetes. Of them, only the Japanese cohort study revealed a clear decreasing trend of type 2 diabetes with increasing dietary intake of vitamin D (9). The other two studies did not reveal any significant relationship between the total intake of vitamin D and incidence of type 2 diabetes.

Several interventional studies have studied the effects of vitamin D supplementation on the development of type 2 diabetes. Pittas *et al,* (2007) administered 700IU vitamin D_3 in combination with calcium 500mg or placebo daily for 3 years for healthy adults and found that among participants

with IFG those who took combined vitamin D and calcium supplements had a lower rise in fasting plasma glucose level (p=0.042) and a lower rise in HOMA-IR (p=0.031) at 3 years compared to those on placebo. Butamong those who had normal fasting glycaemia there was no difference in the change of FPG and HOMA IR (4).

Von Hurst *et al,* (2009) showed a significant improvement in insulin sensitivity, fasting Insulin and insulin resistance with vitamin D supplementa--tion over placebo in non-diabetic, insulin resistant South Asian women after supplementation of 4000IU of vitamin D_3 for a 6 months. (Insulin sensitivity increased p= 0.01, fasting insulin decreased p=0.02, Insulin resistance decreased p=0.03) (10). Several other interventional studies carried out in participants with normal glycaemic level found no significant effect of vitamin D supplementation on fasting plasma glucose level and insulin resistance. (Niles L. 1984, de Bore *et al*, 2008, Avenell *et al*, 2009) (11-13).

Bin-Abbas *et al* and Janner M *et al,* found the prevalence of vitamin D deficiency among children and adolescent with diabetes to be high (14,15). Further, Hypponen *et al* in their birth-cohort study showed a decreased frequency of type 1 diabetes with regular vitamin D supplementation. (OR 0.12, 95%, 0.03 - 0.51) and concluded that vitamin D supplementation in infants could help prevent or reverse the incidence of type 1 diabetes (16) and the EURODIAB Study also concluded that vitamin D supplementation in infancy is associated with a decreased risk of type 1 diabetes, (OR - 0.67 in 95% 0.53 - 0.86) (17).

Case-control studies done by Stene LC, *et al* (2000 and 2003) found that when mothers consumed cod liver oil, (a known vitamin D supplement) during pregnancy their offspring had a lower risk of diabetes (OR - 0.30 in 95% CI 0.12 to 0.75) (18,19). Also the use of cod liver oil during the first year of life may reduce the risk of type 1 diabetes. (OR - 0.74 in 95% CI 0.56 to 0.99) (20).

Complications

Although the association between vitamin D and diabetes has been studied in several observational and interventional studies, evidence for the association between complications of diabetes and vitamin D are sparse. A cross-sectional study carried out by Massimo C *et al,* (2005) found that the prevalence of cardiovascular disease among diabetics is greater when they have co-exsistant hypovitaminosis D (Odds ratio 1.70 in 95%, CI 1.1-2.6, p-0.01) (21). Furthermore, two randomized controlled trials by Sugden JA *et al,* (2007 and 2010) showed a significant improvement in Flow mediated vasodilation (a tool of assessing endothelial function) in the vitamin D received group compared to the placebo group (22,23). Measurement of endothelial function is a surrogate marker to assess cardiovascular risk, especially atherosclerosis (24).

Another study showed a clinically and statistically significant reduction in systolic blood pressure among vitamins D supplemented group than in the placebo group after 8 weeks of therapy (25). No significant changes were found, however, with vitamin D supplementation on HbA1c or insulin resistance even with higher doses of vitamin D3 (26).

Few studies have assessed the association of vitamin D with diabetic neuropthy. Paul Lee *et al* in 2010 showed that patients with type 2 diabetes who have low vitamin D levels had distressing neuropathic pain according to a visual analogue scale (VAS) and pain scores for both the VAS (r^2=0.10) and McGill pain questionnaire (MPQ r^2=0.18). Repletion of vitamin D with mean oral daily dose of 2059IU for 3 months resulted in a significant reduction in pain scores on both the VAS and MPQ, -48.5% and -39.4%, respectively (27). A similar study by Soderstrom L. Hrevealed that vitamin D insufficiency is associated with the self-reported peripheral neuropathy even after adjusting for demographic factors, medications and diabetes duration (28). Shehab D *et al,* also showed that vitamin D deficiency is an independent risk factor of diabetic neuropathy among patients with established diabetes. A greater proportion (81.5%) of patients with diabetic neuropathy had vitamin D deficiency compared to patients without neuropathy (60.4%) and diabetic peripheral neuropathy associated with vitamin D deficiency. (OR - 3.47: CI 1.04 - 11.56, p=0.043) (29).

Nephropathy

The potential relationship between thevitamin D and diabetic retinopathy has been the focus in several cross sectional studies. In 2000, Aksoy H *et al* reported that mean 1, 25 (OH_2) D3 concentration fell with increasing severity of diabetic retinopathy. (DR) (background DR 63.4 $\pm$ 17.26 pmol/L, pre-proliferative DR 47.7 $\pm$ 13.27 pmol/L and for proliferative DR 43.1 $\pm$ 19.45 pmol/L). They also found that, compared to the control group, serum 25 (OH) D concentration was lower in diabetic patients (30). A similar study by Patricia A *et al,* also reported the same results which the percentage of individuals with vitamin D deficiency increased with the severity of retinopathy. But the regression analysis of retinopathy severity vs serum 25-hydroxyvitamin D did not reveal a statistically significant relationship between the two variables (31). Alam *et al,* evaluated the relationship between the two variables and found that there was no difference in serum 25-hydroxyvitamin D concentration between diabetic retinopathy group and the diabetic non-retinopathy group (32). Although most of the studies showed a increased vitamin D deficiency with the severity of the diabetic retinopathy, none of the studies have shown a statistically significant difference between the two variables.

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Vitamin D and mortality in Diabetes

Emerging evidence suggest that inadequate vitamin D may influence the mortality in chronic diseases, especially diabetes. Christel *et al,* followed up 227 patients with type 1 diabetes and during the follow up 44 (18%) patients died, 81 (37%) patients developed microalbuminuria, 27 (12%) developed macroalbuminuria and furthermore 192 (87%) patients developed retinopathy. The hazard ratio of mortality in subjects with severe vitamin D deficiency was 2.7 (95% CI : 1.1 to 6.7). They concluded that severe vitamin D deficiency independently predicts all causes of mortality in patients with type 1 diabetes but not the development of microvascular complications (33). Cristel J *et al,* showed increased all cause mortality among patients with severe vitamin D deficiency during the follow up of 289 patients with type 2 diabetes. (Hazard ratio was 1.96 with 95% CI 1.29-2.98) (34).

Summary

Previous studies have shown a significant association between serum vitamin D status and the incidence of type 2 diabetes. But the dietary vitamin D intake did not show a significant reduction of diabetes incidence. However, in clinical trials, vitamin D supplementation showed a marked improvement of insulin sensitivity and fasting insulin levels in people with insulin resistance but not in people with normal glucose tolerance. However few case control studies have shown that vitamin D supplementation during pregnancy and first year of life could reduce the incidence of type 1 diabetes.

Intervetional studies showed an association between cardiovascular disease and hypovitaminosis D. Few clinical trials also reported a significant improvement of endothelial function resulting in lower systolic blood pressure with vitamin D supplementation in type 2 diabetes.

Vitamin D therapy probably exerts beneficial effects on diabetic microvascular complications as well. Several cross sectional and longitudinal studies have reported an inverse association between serum vitamin D3 level and neuropathic pain and the severity of diabetic retinopathy. Studies have reported that severe vitamin D deficiency is associated with increased mortality in patients with both types of diabetes. Considering above results a hypothesis can be developed that vitamin D status is a significant determinant of the incidence, occurrence of complications, and the all cause mortality of diabetes.

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