

Links between Vitamin D deficiency and diabetes-associated macrovasculopathy

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In the editorial of the current issue of the South East Asia Journal of Public Health, Brown *et al.*¹ highlighted the effects of Vitamin D deficiency and *pros* and *cons* of using Vitamin D supplementation to treat the deficiency. In this editorial, the links between Vitamin D deficiency and diabetes-associated macrovasculopathy will be discussed. Research has linked inadequate Vitamin D status to macrovascular diseases in Type 2 diabetes (T2DM).^{2,3} The key aspects of pathophysiology that explains the link between Vitamin D deficiency and macrovasculopathy include: pancreatic β -cell dysfunction, peripheral insulin resistance, chronic inflammation, and endothelial dysfunction.⁴ Diabetic macrovasculopathy is associated with structural and functional changes in large arteries, which causes endothelial dysfunction, increased arterial stiffness, or decreased arterial distensibility.⁵ However, there remains a paucity of large long-term randomized clinical trials showing link between Vitamin D deficiency and macrovasculopathy in T2DM patients.

Type 2 diabetes (T2DM) is a chronic, degenerative and non-communicable disease, it is associated with a high prevalence of cardiovascular (CV) morbidity and mortality.⁶ The estimated prevalence of T2DM worldwide for 2015 has risen to 415 million from 151 million in 2000, and the total number of people with diabetes is projected to rise to 642 million by 2040.^{7,8} According to IDF, approximately one-fifth (78.3 million) of all adults with T2DM in the world live in the South-East Asia Region.⁸ Current estimates indicate that 8.5% of the adult population in the region have diabetes, and India is home to the second largest number of diabetic patients in the world, after China.⁸ IDF also forecasted that the number of people with T2DM in the region will increase to 140.2 million by 2040. Type 2 diabetes is a global epidemic with a devastating human, social, and economic impact. The costs of diabetes are enormous; both for health care services and through loss of productivity.⁶ The majority of countries in the world spend between 5-20% of their total health expenditure on T2DM.⁸ Approximately 12% of the health budget of the South-East Asia Region account for treatment of diabetes. With such a high cost, T2DM poses a formidable challenge for healthcare systems and a barrier to sustainable economic development.⁸

It is estimated that up to 80% of the global diabetic

population of 200 million will die of cardiovascular disease (CVD).⁹⁻¹¹ Type 2 diabetes acts as an independent risk factor for several forms of CVD, and people with T2DM are 2-4 times more likely to develop CVD due to a variety of risk factors.^{5,12} The complications of diabetic vasculopathy are commonly grouped into microvascular and macrovascular complications.¹³ The most important forms of CVD are coronary heart disease, cerebrovascular disease, and peripheral vascular disease. These lead to heart attacks, angina, heart failure, stroke, and gangrene or ulceration of the feet and legs requiring amputation. In diabetes, macrovascular complications are the commonest cause of morbidity and mortality.¹³

Vitamin D insufficiency is now recognized as a common public health problem of increasing prevalence worldwide, very often unrecognized and untreated, associated with musculoskeletal diseases.¹⁴ It is estimated that 30% to 50% of the world's population suffers from Vitamin D deficiency, with over one billion people affected.¹⁵ In the UK, it was reported that 91% of patients with T2DM had a Vitamin D deficiency, with a severe deficiency in 32% of patients.¹⁶ The connection between the lack of Vitamin D and a number of diseases including CVD is also well established. Vitamin D has some antiatherogenic functions and its deficiency is considered a marker of CV risk which promotes accelerated atherosclerosis by enabling vascular inflammation, endothelial dysfunction, formation of foam cells, and proliferation of smooth muscle cells.^{17,18} It was demonstrated that long-term deficiency also causes metabolic syndrome and T2DM due to development of secondary hyperparathyroidism, increasing insulin resistance, and impaired β -pancreatic cell function.¹⁹ Vitamin D deficiency also causes arterial stiffness, which is considered a predictor of CV morbidity and mortality²⁰ and a marker of subclinical atherosclerosis.^{9,11,18}

Research studies have suggested associations between CVD and Vitamin D deficiency,²¹⁻²⁷ but most of these studies have been experimental or cross-sectional. The Framingham Offspring Study reported that subjects with a severe Vitamin D deficiency (and no prior diagnosis of CVD) experienced a hazard ratio of 1.80 for developing their first CV event 5 years after their follow-up compared to subjects with higher levels of Vitamin

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D.²⁴ The Health Professional Follow-Up Study examined the Vitamin D levels in nearly 50,000 men without prior CVD, and then followed them for 10 years.²¹ They found that men who were deficient in Vitamin D showed a two-fold increase in the rate of myocardial infarction. Other studies have found that low Vitamin D levels were associated with a higher risk of heart failure, sudden cardiac death, stroke, overall CVD, and CV death.^{22,23,25} Two large-scale randomized trials ($n \geq 10,000$ participants; duration 5 years) of Vitamin D supplementation with the primary endpoint as CVD and cancer are ongoing which include: VITAL, U.S. (recruitment completed)²⁸ and the Finnish Vitamin D trial (FIND), Finland (Recruiting).²⁹ The outcomes of these trials will provide more evidence regarding the use of Vitamin D supplements in treating CVD and its associated complications.

Previous reports suggested that the risk for T2DM³⁰⁻³² and diabetic microvasculopathy^{2,3} increases with Vitamin D deficiency; however, the links between Vitamin D deficiency and macrovasculopathy in diabetic patients remains unclear.⁴ A meta-analysis conducted by Pittas *et al.*³⁰ identified that Vitamin D deficiency was common in diabetic patients, and Vitamin D supplementation could delay or prevent diabetic complications. Another meta-analysis has demonstrated an inverse association between circulating 25-hydroxy vitamin D [25(OH)D] and the incidence of T2DM.³³ The credible mechanism of this analysis explained an association between Vitamin D receptors in pancreatic beta-cells on insulin secretion, Vitamin D effects on insulin sensitivity, and its effects on calcium metabolism. However, the causality of the effects have not yet demonstrated.³³⁻³⁵ A recent 5-year observational study, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study,⁴ demonstrated an inverse association, independent of treatment and duration of diabetes, between the serum concentration of 25(OH)D and macrovascular diseases. A 25(OH)D concentration < 20 ng/mL had a higher cumulative incidence of macrovascular events than those with levels ≥ 20 ng/mL. It was also found that higher baseline blood 25(OH)D was associated with reductions in the risk of macrovascular disease by 20% per 50 nmol/L, which, after adjustment for classical risk predictors, including HbA_{1c}, became 23%.

Blood 25(OH)D may be considered as an independent predictor for macrovascular events in people with T2DM.⁴ Serum 25(OH)D testing, which is less expensive and non-invasive, can be used as an effective measuring tool for macrovascular diseases in people with T2DM. Rigorous large-scale supplementation trials are needed to study underlying mechanisms of the relationship between serum concentration of 25(OH)D and macrovascular disease in T2DM patients. Further research should be conducted to demonstrate the effect of Vitamin D on diabetes associated pancreatic tissue and cells of the immune system, Vitamin D binding proteins, Vitamin D metabolism and Vitamin D receptors, glucose intolerance, insulin secretion and sensitivity, and inflammation.³³ As Vitamin D plays an

important role in glycemic control, this may influence cardiovascular outcomes including macrovascular diseases.³⁵

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