

## Effect of vitamin D on insulin resistance and nephropathy in type 2 diabetes

Sir,

Diabetic kidney disease is a major risk of end-stage renal disease. Many complex factors are associated with the progression of diabetic nephropathy. Recently, much attention has been directed toward the role of vitamin D in the insulin resistance and treatment of diabetic nephropathy.<sup>[1]</sup> Heshmat *et al.*, conducted a randomized double-blind clinical trial to find out the effect of vitamin D on insulin resistance and anthropometric parameters in type 2 diabetes mellitus (T2DM).<sup>[2]</sup> They included 42 diabetic patients with similar baseline characteristics in two groups; intervention group with single intramuscular injection of 300,000 IU of vitamin D3 and placebo group. In their study, 3 months after vitamin D injection, HbA1c, anthropometric factors, and homeostasis model assessment index in the intervention group remained constant while, serum 25-hydroxy vitamin D3 (25 (OH) D3) significantly increased. They assumed that a single injection of vitamin D was not accompanied with improvement of diabetes control and insulin resistance.<sup>[2]</sup> It was suggested that vitamin D, was a negative regulator of the circulating and local tissue renin-angiotensin system, whereas the renin-angiotensin system has a significant role in the physiology of sodium and volume homeostasis.<sup>[3-6]</sup> Excess activity of the renin-angiotensin system is associated with renal disease, diabetes, and high blood pressure.<sup>[3-6]</sup> Indeed, it is possible that the most important putative mechanisms associating vitamin D to control blood glucose are regulation of the renin-angiotensin system and suppression of renin biosynthesis.<sup>[2-5]</sup> Notably, the circulating and intra-pancreatic renin-angiotensin levels have been found to negatively influence  $\beta$ -cell function and peripheral insulin sensitivity.<sup>[2-7]</sup> In agreement to this study, we conducted a double-blind randomized clinical trial on 60 T2DM patients who were divided into two groups with 30 patients in each. Serum 25 (OH) D level was measured with ELISA method. Patients were given weekly vitamin D supplementation (50,000 units) for 12 weeks. In this investigation, there was no significant relation between HbA1c and 25 (OH) D levels prior the study. After treatment, 25 (OH) D level in interventional group significantly increased compared to that of the control group. The

HbA1c concentration in male interventional group is significantly less than that of the control group.<sup>[7]</sup> We concluded that weekly vitamin D supplementation had beneficial effects on glycemic parameters in male T2DM patients.<sup>[6]</sup> Study regarding the glycemic control of vitamin D revealed different results. Recently, in a study conducted by Huang *et al.*, the difference in vitamin D levels between those with micro-and those with macro-albuminuria was examined.<sup>[7]</sup> They also aimed to determine whether low dose of cholecalciferol was able to ameliorate albuminuria. They conducted two investigations; a cross-sectional study of patients with T2DM and healthy controls and a longitudinal study on T2DM patients with albuminuria treated with conventional dose (800 IU) of cholecalciferol for 6 months.<sup>[7]</sup> In the first study, compared to controls and T2DM patients with normoalbuminuria, the serum 25 (OH) D3 level was significantly lower in patients with macro-albuminuria, but not in patients with micro-albuminuria. They detected that plasma 25 (OH) D3 level was independently associated with micro-albuminuria. In their longitudinal investigation, they found that cholecalciferol efficiently decreased micro-albuminuria in the early stages of treatment in conjunction with an increase in serum 25 (OH) D3 level.<sup>[7]</sup> They interpreted that conventional doses of cholecalciferol might have an anti-proteinuric effect on Chinese T2DM patients with nephropathy.<sup>[7]</sup> Furthermore, they found that a low vitamin D status was more closely associated with micro-albuminuria in male subjects than in female ones.<sup>[7]</sup> Limitations of the study conducted by Heshmat *et al.* need to be considered, too. The sample size was small and the duration of drug therapy was short. Notably, the season may affect vitamin D level and also may have an impact on the treatment outcome, a factor that is very difficult to control.<sup>[7-10]</sup> In addition, the best effective dose requires further investigation.<sup>[10-14]</sup> Lastly, the lack of assessment of parathormone level is a deficit. There is an evidence revealing the positive association of parathyroid hormone and level of blood pressure as a perturbing factor for diabetic nephropathy.<sup>[2-9,15-18]</sup> Thus, the negative result on improving diabetes control and insulin resistance should not discourage its use. We suggest more prospective interventional investigations with longer duration with control of confounders to better detect this aspect of diabetic patients. Furthermore, it should be reminded that the most effective dose of vitamin D requires further examination.

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