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Mini-Review

Vitamin D therapy in diabetic kidney disease; current knowledge on a public health problem

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Abstract

Diabetic kidney disease is a major risk of end-stage kidney failure and is associated with great morbidity and mortality, predominantly with accelerated cardiovascular disease. Current investigations have focused on the optimization of renin-angiotensin system blockade in patients with diabetic kidney disease using combinations of drugs that target this pathway, however some studies have focused on the potential of novel treatments that either target various pathways up-regulated by hyperglycemia or other targets believed to promote progression of diabetic kidney disease such as endothelin system, inflammation and vitamin D receptors. So far, a strong body of evidence supports vitamin D as a negative regulator of the circulating and local tissue renin-angiotensin system, while the renin-angiotensin system have a critical role in the physiology of sodium and volume homeostasis. The results of oral vitamin D therapy in type 2 diabetic patients are encouraging. However, more prospective interventional studies with larger duration and control of confounders are suggested.

Keywords: Vitamin D, Diabetic kidney disease, Renin-angiotensin system

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Introduction

Diabetic kidney disease is a major risk of end-stage kidney failure (1) and is associated with great morbidity and mortality, predominantly with accelerated cardiovascular disease (2,3). Various complex factors are related to the progression of diabetic kidney disease (4,5). Current investigations have focused on the optimization of renin-angiotensin system blockade in patients with diabetic kidney disease using combinations of drugs that target this pathway (2-8), however some studies have focused on the potential of novel treatments that either target various pathways up-regulated by hyperglycemia or other targets believed to promote progression of diabetic kidney disease such as endothelin system, inflammation and vitamin D receptors (9-11).

Vitamin D and diabetic nephropathy

A strong body of evidence supports vitamin D as a negative regulator of the circulating and local tissue renin-angiotensin system, while the renin-angiotensin system have a critical role in the physiology of sodium and volume homeostasis (8-11). Excess activity of the renin-angiotensin system is associated with high blood pressure, renal disease and diabetes. Indeed it is possible that the most important putative mechanisms associating vitamin D to blood glucose control are regulation of the renin-angiotensin system and suppression of renin biosynthesis (4-8). Interestingly, the circulating and intra-pancreatic renin-angiotensin levels are known to negatively influence β-cell function and peripheral insulin sensitivity. It is hypothesized that down-regulation of the renin-angiotensin system by vitamin D may arbitrate its beneficial properties on glycemic control and diabetes (8-11). Current attitudes to the prevention of diabetic kidney disease comprise the strict control of blood glucose and blood pressure. The rigorous control of blood glucose,

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Implication for health policy/practice/research/ medical education

Diabetic kidney disease is a major risk of end-stage kidney failure and is associated with great morbidity and mortality, predominantly with accelerated cardiovascular disease. Various complex factors are related to the progression of diabetic kidney .The results of oral vitamin D therapy in type 2 diabetic patients are encouraging .However, more prospective interventional studies with larger duration and control of confounders are suggested.

as quickly as possible, was shown to be effective in most of clinical trials. However, the pathogenesis of diabetic kidney disease seems to be multifactorial. Various genetic and environmental factors are expected to contribute to its development and progression (2-10). It seems that treatment with vitamin D analogues reduces the urinary urine albumin/creatinine ratio level by suppressing the compensatory renin increase in type 2 diabetic patients (8-11). These beneficial effects might be contributed to suppressed kidney expression of renin and TGF-β which may or may not be angiotensin II dependent (9-15). Epidemiological investigations have shown that low 25(OH) D3 levels are common in individuals with albuminuria. In a study on 60 type 2 diabetic patients, we found five patients had vitamin D deficiency (8.3%) and 27 (45%) had insufficient levels of vitamin D (16). Recent studies have shown that paricalcitol as a selective vitamin D receptor activator, efficiently reduces proteinuria in subjects with type 2 diabetes melli tus who have been treated with renin-angiotensin system inhibitors (3-11). In a randomized double blinded clinical trial on 60 patients (30 patients; control group and 30 patients as interventional group), we recently found that weekly vitamin D supplementation (cholecalciferol; 50,000 units) for 12 weeks , had beneficial effects on glycemic parameters in male type 2 diabetic patients (16). Similar doses also were moderator of blood pressure, too (17). Hence, the anti-proteinuric property of vitamin D in diabetic nephropathy seems to be due to its 'non-classical' properties, which are distinct to its role in mineral metabolism. Indeed, the 'non-classical' influences are mediated by vitamin D receptor activation (14-19). Evidence suggests that the effect of vitamin D receptor activation is partly that of negatively regulating renin-angiotensin system, which plays a critical role in the development of diabetic nephropathy (4-10). In a study conducted by Huang *et al*, the differences in vitamin D levels between those with micro- and those with macro-albuminuria were examined (19). They also sought to determine whether low dose of cholecalciferol was able to ameliorate albuminuria. They conducted two studies, a cross-sectional study of patients with type 2 diabetes mellitus and healthy controls and a longitudinal study on type 2 diabetes mellitus patients with albuminuria treated with conventional doses (800 IU) of cholecalciferol for 6 months having a control group (19). In the first study, compared to controls and type 2 diabetes mellitus patients with normoalbuminuria, serum 25(OH) D3 levels were significantly lower in patients with macro-albuminuria, but not in those with micro-albuminuria. They found that plasma 25(OH) D3 levels were independently correlated with micro-albuminuria. In their longitudinal study, they found cholecalciferol efficiently decreased micro-albuminuria in the early stages of treatment in conjunction with an increase in serum 25(OH) D3 levels (19). They concluded that, conventional doses of cholecalciferol might have antiproteinuric effects on Chinese type 2 diabetic patients with nephropathy (19). Also, they found that a low vitamin D status was more closely associated with micro-albuminuria in male subjects than in females (19). However, it should be noted that the most effective dose needs further exploration. Recently, Bonakdaran *et al.* conducted a study to assess the effects of vitamin D therapy on albuminuria in type2 diabetes patients. They conducted this cross-sectional study on 119 outpatients with type-2 diabetes. Patients with vitamin D deficiency/insufficiency received calcitriol (1, 25-dihydroxycholecalciferol; 1, 25-dihydroxyvitamin D3) therapy for eight weeks. They observed a significant correlation between 25 (OH) D levels and presence of micro-albuminuria (20). Also they showed that therapy with calcitriol had none significant decrease on the albumin excretion rate. However, the effects of calcitriol on reduction of diastolic blood pressure, glycosylated hemoglobin and levels of total cholesterol were observable (20). Similar effect of cholecalciferol on the level of blood pressure was also observed in our recent clinical trial on 60 type 2 diabetic patients (17). Encouraging results have also been found in animal studies. It has been observed that vitamin D analogs are able to inhibit mesangial cell proliferation, suppress renin expression (14-16), reduce glomerulosclerosis and increase the expression of fibrogenic markers (14-16). In an experimental study on diabetic rats, Nakai *et al.* found that maxacalcitol, as an active vitamin D analog, was able to reduce albuminuria and mesangial matrix expansion. They suggested that maxacalcitol attenuates the progression of diabetic kidney disease by suppression of oxidative stress (21). Previously Kim et al, observed that oral cholecalciferol was able to decrease albuminuria and urinary TGF-β1 in subjects with type 2 diabetic nephropathy on established renin-angiotensin-aldosterone system inhibition (22).

Conclusion

The results of oral vitamin D therapy in type 2 diabetic patients are encouraging (23-26). However, more

prospective interventional studies with larger duration and control of confounders are suggested.

Authors' contributions

All authors wrote the paper equally

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Conflict of interests

The authors declared no competing interests.

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