

## Editorial Comment

# Vitamin D: something new under the sun

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Cardiovascular (CV) disease is the major cause of death in the general population and in chronic kidney disease (CKD) patients. In particular, the CV morbidity and mortality rate is highly prevalent in CKD patients because of frequently concomitant hypertension, peripheral vascular disease, heart failure, vascular calcification (VC), diabetes and mineral bone disease (CKD-MBD). More recently, a 'relatively' new emerging factor that is strongly associated with CV risk in CKD patients has been recognized and investigated: vitamin D deficiency [1].

Our understanding of the biological effects of the vitamin D system has evolved considerably in recent years, with the identification of 25-hydroxyvitamin D (25-D) and 1,25-dihydroxyvitamin D (1,25-D) as hormones with 'pleiotropic' effects beyond mineral metabolism and parathyroid hormone (PTH) control in CKD patients [2]. Indeed, recent studies have been proposed and realized to investigate the effects of either native 25-D or active 1,25-D on the CV and renal systems [3].

I read with interest the article by Loh *et al.* [4] in this issue of the journal regarding the association of lower serum 25-D levels and the prevalence of diabetes and absence of native vitamin D supplementation in 219 CKD patients in Singapore. Considering that Singapore is a country where exposure to sunlight is adequate, it may be surprising to learn that 25.6% of the observed CKD patients showed serum 25-D levels <16 ng/mL. As it is nearly impossible to get adequate amounts of vitamin D from their diet (mushrooms, eggs and fish), sunlight exposure is the only reliable way to generate vitamin D. Even in such a sun-rich country as Singapore, vitamin D deficiency is high in CKD patients. Do we have a solution to this problem?

The 'optimal' vitamin D levels remain to be determined; however, the definition of 'vitamin D deficiency' when 25-D levels fall <20 ng/mL (~50 nmol/L) should be generally accepted.

Vitamin D receptors (VDRs) are present in several (probably all) systems and tissues (Figure 1) and VDR activation is associated with positive effects, such as better blood pressure control and prevention of diabetic nephropathy. Systemic activation of VDRs, as suggested by observational studies, may decrease CV mortality in the general population and especially in patients affected by renal failure [5]. Moreover, a meta-analysis of randomized trials analysing the impact of vitamin D among patients with different health conditions demonstrated that vitamin D intake reduces the all-cause mortality rates [6].

In a prospective study, men with vitamin D deficiency (25-D levels <15 ng/mL) showed an increased risk of myocardial infarction [5]: it was proposed that VDR signalling had a possible anti-hypertrophic action. Vitamin D deficiency was also found to be associated with an increased pulse wave velocity and arterial stiffness along with increased left ventricular hypertrophy and CV mortality in dialysis patients [7, 8]. Some clinical studies showed an inverse relationship between the circulating vitamin D levels and blood pressure and/or plasma renin activity, but the mechanism is unclear [9].

Nevertheless, CKD patients present a condition of chronic inflammation involving the CV system and a reduced immunity to infections. Evidence from several studies demonstrated a possible role of vitamin D as an immuno-modulatory and anti-inflammatory agent [10]. Non-specific microinflammation, characterizing CKD patients, has been investigated as a risk factor involved in the pathogenesis of accelerated atherosclerosis and VC. In fact, CKD patients affected by vascular or valvular calcification have higher serum levels of various markers of inflammation, such as C-reactive protein and *tumor necrosis factor* (TNF)- $\alpha$  or interleukin-6 (IL-6) [11].

The link between vitamin D deficiency and CV morbidity and mortality is currently arousing great interest. In CKD patients, this association is even stronger, because VDR activation decreases as a result of progressive renal impairment. In fact, a poor vitamin D status in CKD patients is a risk factor for CV mortality. Haemodialysis patients with very low levels of 25-D and 1,25-D are at a significantly increased risk of early CV mortality, including sudden cardiac arrest [12, 13]. Furthermore, in non-dialysis CKD patients this increased risk still persists with severely deficient 25-D levels <10 ng/mL showing an almost 6-fold higher risk of mortality than patients with adequate levels ( $\geq 30$  ng/mL) [14].

Most importantly, native vitamin D supplementation with ergocalciferol or cholecalciferol has been associated with a significant reduction in total mortality by 7% compared with placebo [6]. Therefore, accordingly with the Kidney Disease: Improving Global Outcome guidelines 25-D testing should be routine in CKD patients and they should be re-tested after 3 months of supplementation, aiming for a level of at least 30 ng/mL [15].

Although native (or dietary) vitamin D supplementation can replenish 25-D levels in CKD, there is also a need for VDR activation therapy (calcitriol or selective VDR activators) to correct abnormally low levels of 1,25-D and to control serum PTH levels [16, 17].

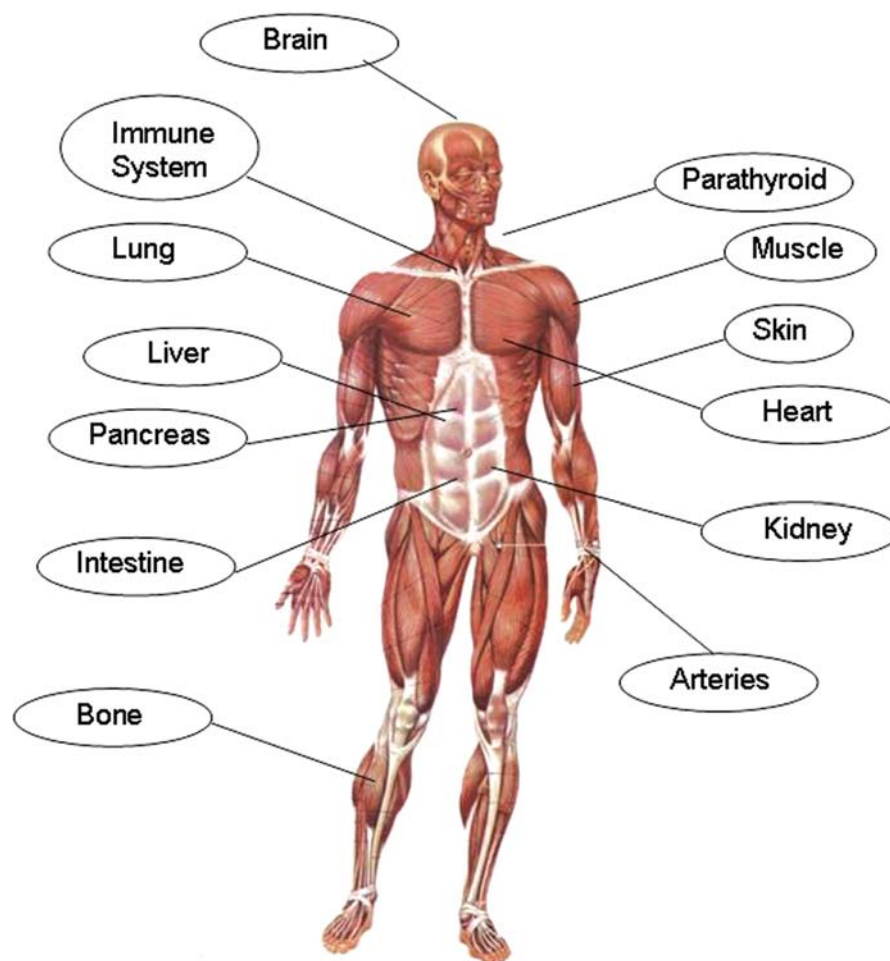


Fig. 1. Vitamin D receptor distribution in human organs and tissues.

In conclusion, because the CV system is a major target tissue for vitamin D, CKD patients with a poor 25-D status are at elevated risk of CV mortality [18]. Native vitamin D may reduce CV events and mortality, even if, at present, no sufficient outcome data can confirm this. Large randomized controlled trials should elucidate this apparent benefit of CV risk reduction and mortality in CKD patients treated with vitamin D.

*Conflict of interest statement.* None declared.

(See related article by Loh *et al.* Clinical and demographic predictors for vitamin D deficiency in multiethnic Asian patients with chronic kidney disease. *Clin Kidney J* 2012; 5: 303–308)

## References

1. Cozzolino M. The calciotropic hormones PTH and vitamin D: from bone to blood vessels. *J Intern Med* 2012; 271: 566–568
2. Ebert R, Schütze N, Adamski J *et al.* Vitamin D signaling is modulated on multiple levels in health and disease. *Mol Cell Endocrinol* 2006; 248: 149–159
3. Cozzolino M, Ketteler M, Zehnder D. The vitamin D system: a crosstalk between the heart and kidney. *Eur J Heart Fail* 2010; 12: 1031–1041
4. Loh ZY, Yap CW, Vathsala A *et al.* Clinical and demographic predictors for vitamin D deficiency in multiethnic Asian patients with chronic kidney disease. *Clin Kidney J* 2012; 5: 303–308
5. Giovannucci E, Liu Y, Hollis BW *et al.* 25-Hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med* 2008; 168: 1174–1180
6. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2007; 167: 1730–1737
7. London GM, Guerin AP, Verbeke FH *et al.* Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency. *J Am Soc Nephrol* 2007; 18: 613–620
8. Thadhani R, Appelbaum E, Chang Y *et al.* Vitamin D receptor activation and left ventricular hypertrophy in advanced kidney disease. *Am J Nephrol* 2011; 33: 139–149
9. Tian J, Liu Y, Williams LA *et al.* Potential role of active vitamin D in retarding the progression of chronic kidney disease. *Nephrol Dial Transplant* 2007; 22: 321–328
10. Alborzi P, Patel NA, Peterson C *et al.* Paricalcitol reduces albuminuria and inflammation in chronic kidney disease. A randomized double-blind pilot trial. *Hypertension* 2008; 52: 249–255
11. Eleftheriadis T, Antoniadi G, Liakopoulos V *et al.* Paricalcitol reduces basal and lipopolysaccharide-induced (LPS) TNF- $\alpha$  and IL-8 production by human peripheral blood mononuclear cells. *Int Urol Nephrol* 2010; 42: 181–185
12. Wolf M, Shah A, Gutierrez O *et al.* Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney Int* 2007; 72: 1004–1013

13. Drechsler C, Verduijn M, Pilz S *et al.* Vitamin D status and clinical outcomes in incident dialysis patients: results from the NECOSAD study. *Nephrol Dial Transplant* 2011; 26: 1024–1032
14. Pilz S, Tomaschitz A, Friedl C *et al.* Vitamin D status and mortality in chronic kidney disease. *Nephrol Dial Transplant* 2011; 26: 3603–3609
15. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl* 2009: S1–S130
16. Brancaccio D, Cozzolino M, Cannella G *et al.* Secondary hyperparathyroidism in chronic dialysis patients: results of the Italian FARO survey on treatment and mortality. *Blood Purif* 2011; 32: 124–132
17. Cozzolino M, Brancaccio D, Cannella G *et al.* VDRA therapy is associated with improved survival in dialysis patients with serum intact PTH  $\leq 150$  pg/mL: results of the Italian FARO Survey. *Nephrol Dial Transplant* 2012; doi:10.1093/ndt/gfs108
18. Cozzolino M, Stucchi A, Rizzo MA *et al.* Vitamin D receptor activation and prevention of arterial ageing. *Nutr Metab Cardiovasc Dis* 2012; 22: 547–552

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