INVITED COMMENTARY

The Quest for the Culprit Responsible for Arteriovenous Fistula Maturation Failure

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In this issue, Kubiak et al. report on 562 patients with chronic kidney disease (CKD) undergoing single stage surgical creation of an autologous upper extremity arteriovenous fistula (AVF).[1] This was actually a sub-study of the somewhat larger Haemodialysis Fistula Maturation Study, with the aim of testing the association between mineral metabolism markers (MMMs) and histology of vein samples obtained at AVF creation and also unassisted and overall clinical AVF maturation. MMMs included fibroblast growth factor-23, parathyroid hormone, calcium, phosphate, and the vitamin D metabolites $1,25(OH)_2D$, $24,25(OH)_2D$, 25(OH)D, and bioavailable 25(OH)D. The rationale behind the study was that MMMs could affect AVF maturation because they are known to affect arterial stiffness in early CKD.

The authors should be commended on their rigorous methodology involving core laboratory measurements of MMMs and histology, but also a very rigid definition of AVF maturation, recently renamed "AVF functionality."[2]

Despite the efforts made to complete the study, there was no association between MMM levels, except for one of them, and any of the predefined outcomes. A 17% greater risk of overall AVF maturation failure per 0.5 ng/dL higher serum $24,25(OH)_2D$ concentration was reported, which may well be the result of multiple testing leading to a type I error.

The results of this study have been put properly into perspective. However, some additional discussion may enhance the clarity of its findings. In a previous cross sectional report from the Haemodialysis Fistula Maturation Study,[3] vitamin D metabolites were not associated with flow mediated dilation. Also, higher serum concentrations of bioavailable vitamin D and 1,25-dihydroxyvitamin D were associated with 0.62% and 0.58% greater nitroglycerin mediated dilation values, respectively, in basic but not in adjusted models. There were no significant associations between vitamin D metabolites and carotid-femoral or carotid-radial pulse wave velocities. The authors concluded that in CKD patients, serum concentrations of vitamin D metabolites were not associated with vasodilator functions or vascular stiffness.

Furthermore, in a double blind, placebo controlled randomised pilot study on 52 haemodialysis patients scheduled to have AVF creation, peri-operative high dose vitamin D3 (cholecalciferol) was compared with placebo.[4] AVF or haemodialysis graft use at six months was 45% in vitamin D3 treated patients and 54% in placebo treated patients ($p = .8$). Baseline and post-treatment serum concentrations of 25(OH)D and $1,25(OH)_2D$ had no association with AVF or haemodialysis graft maturation.

As the authors have pointed out, successful AVF maturation requires an orderly vascular remodelling process, which involves nitric oxide mediated vasodilation, smooth muscle relaxation, elaboration of matrix metalloproteinases, digestion of the internal elastic lamina, and local inhibition of platelet aggregation. Others have suggested research into physical factors involved in the pathophysiology of vessel enlargement.[5] It is plausible to postulate that further research into these physiological processes may elucidate further the pathophysiology of AVF maturation failure, potentially leading to pre-emptive or therapeutic strategies aimed at improving the functionality of the AVF, largely considered to be the "line of life" for CKD patients.

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