Arterial ^{18}F -NaF-uptake as a marker for vascular calcification activity. Can a little salt cut the sweet: a golden bullet to evaluate vascular mineralization?

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In this issue of the Journal of Nuclear Cardiology, Bellinge and colleagues from the University of Western Australia have investigated the effect of vitamin-K₁ and colchicine on vascular calcification activity in a randomized fashion.¹ In 154 patients with diabetes mellitus and present coronary calcification, they demonstrate that treatment with vitamin-K₁ and/or colchicine did not lead to a reduction in vascular calcification activity, as measured with ^{18}F -sodium fluoride (^{18}F -NaF) PET/CT. In fact, ^{18}F -NaF uptake in both the aorta and coronary arteries did not statically change after the 3-month treatment period in all groups. The authors are to be congratulated on performing this well-matched, double-blind, placebo controlled 2x2 factorial trial, evaluating promising therapies that distinctly target the inflammatory and osteogenic pathways which are deemed to contribute to vascular mineralization.

Editorial to The effect of Vitamin-K1 and Colchicine on Vascular Calcification Activity in subjects with Diabetes Mellitus (ViK-CoVaC); A double-blind 2x2 factorial randomized controlled trial.

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Although the extent of vascular calcifications is strongly related to cardiovascular risk,² no treatment currently exists to halt or impair the process of vascular mineralization.³ Previous trials have shown inconsistent effects of drug therapy: statins for instance are described to either prevent, have no effect, or accelerate vascular calcification. However, these findings may reflect that intervention in various stages of the atherosclerotic disease process can affect the calcification process differently.^{4,5} When intervening before atherosclerosis develops, reducing the amount of apo-B containing lipid-laden particles may prevent calcification from occurring at all. Intervention in later stages may halt active inflammation, allowing encapsulation of established atherosclerotic plaque. On computed tomography (CT), this can translate to a higher calcium score (reflecting increased risk), even though highly calcified plaques have a lower risk of rupturing than low attenuation plaques.

To tackle this issue, researchers have looked at other methods to visualize the process of calcification. The use of ^{18}F -NaF, originally developed as a bone tracer, has been extended to the field of atherosclerosis since the observation that vascular radiotracer accumulation often co-localizes with arterial calcifications.⁶ ^{18}F -NaF exchanges fluoride ions with hydroxyl ions on hydroxyapatite crystals and predicts progression of calcification, independent from baseline calcific burden.^{7,8} Moreover, previous studies have shown that ^{18}F -NaF preferentially adsorbs in areas of microcalcification, reflecting an earlier stage of the disease process which could still be amenable to medical therapy.⁹ However, important to note is that no trials have been able to

demonstrate a reduction in vascular or valvular ^{18}F -NaF uptake after medical intervention yet.

^{18}F -fluorodeoxyglucose (^{18}F -FDG) remains to date the only PET tracer that has been capable of showing a reduction from its baseline arterial wall uptake. Moreover, this observed reduction after treatment initiation generally aligns with clinical trial outcomes. For instance, the clinical benefit of statins, PCSK9-inhibitors, and pioglitazone were all paired with reductions of the ^{18}F -FDG signal within a three- to four-month timeframe.^{10–12} Several negative clinical trial outcomes, such as for dalcetrapib, lipoprotein-associated phospholipase A2 inhibition, and P38 MAP kinase inhibitors, were also in line with the neutral effects on arterial wall inflammation evaluated by ^{18}F -FDG.^{13–15} However, there are also important limitations associated with the use of ^{18}F -FDG, the most important ones being its non-specificity, and difficulty to assess coronary atherosclerosis due to the high myocardial background uptake. A more specific marker capable of assessing treatment effects over a short time period is therefore highly sought-after, but the promise of ^{18}F -NaF being such a marker still has to be delivered.

The finding of Bellinge and colleagues, as reported in this issue of the Journal of Nuclear Cardiology, that neither colchicine nor vitamin- K_1 treatment reduces calcification activity in a timeframe of three months is an important addition to the ^{18}F -NaF literature, but does raise several questions. First, colchicine treatment has been shown to significantly decrease cardiovascular risk through inhibition of the NLRP-3 pathway.¹⁶ Hence, it is reasonable to imagine that colchicine treatment ultimately does ameliorate progression of calcification. For instance, colchicine has previously been shown to favorably modify coronary plaque.¹⁷ ^{18}F -NaF uptake in atherosclerotic plaque is associated with vulnerable plaque characteristics, thus it would be expected that colchicine treatment can attenuate both in a similar fashion. This discrepancy may however be attributed to the difference in treatment duration between these studies: a year versus three months of follow-up. Although inhibition of inflammatory pathways may decrease osteogenic transformation in the long run, it could be that this transition is not visible within a period of three months. The absence of an effect of vitamin- K_1 treatment on vascular ^{18}F -NaF uptake is interesting, as this directly interferes with the osteogenic pathway, thus is less likely to be caused by the relatively short treatment duration. Vitamin K is a vital component for the activation of matrix Gla protein, a potent inhibitor of tissue calcification. Nevertheless, extensive calcifications caused by vitamin K deficiency are mainly considered problematic in hemodialysis patients rather than diabetics, who were included in the current study.

Thus, whether vitamin- K_1 treatment in a population with chronic kidney disease can attenuate vascular ^{18}F -NaF uptake remains to be answered.

Currently, there are several ongoing trials evaluating the effect of drug therapy on ^{18}F -NaF uptake. These studies mainly involve lipid lowering (NCT03233243, NCT03689946, NCT03051360) and modulation of osteogenesis (NCT02839044, NCT02917525, NCT02132026) in atherosclerosis and aortic valve stenosis. We have to wait for the outcome of these trials before we can adequately address the question whether ^{18}F -NaF is useful not only as a tool for the assessment of treatment effects but also if the changes (i.e., reduction) in ^{18}F -NaF uptake are related to improved patient outcomes.

Disclosure

The authors report no conflicts of interest.

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