The Control of Hyperphosphatemia in Renal Failure: Between Vascular Calcification and Inflammation

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In this issue of *Blood Purification*, I read with interest the article by Hauser et al. [1] on the effects of the aluminum- and calcium-free phosphate binder sevelamer carbonate on reducing the levels of tumor necrosis factor α and endotoxin in an experimental model of uremia. The authors' results support one of the potential mechanisms involved in vascular calcification (VC): the role of phosphate in regulating arterial mineralization, in a manner 'similar' to bone formation.

I have really found the manuscript of interest, and I would like to discuss why these results may be important from the clinical point of view, with special attention to chronic kidney disease (CKD) patients.

Accelerated atherosclerosis and VC play a central role in the pathogenesis of cardiovascular disease in CKD patients. Mineral metabolism disorders and increased serum calcium-phosphate product have recently been investigated as inducing factors in cardiovascular calcification [2]. In fact, cardiovascular disease in renal failure appears greatly associated with alterations of bone metabolism. Recently, the treatment of hyperphosphatemia in CKD patients changed from either calcium- or aluminum-based phosphate binders to new calcium- and aluminum-free phosphate binders, such as sevelamer carbonate and lanthanum carbonate. Therefore, control of serum phosphate in CKD patients becomes crucial in

preventing increases in calcium-phosphate product, secondary hyperparathyroidism and ultimately VC.

CKD patients develop extensive medial calcification, which contributes to higher cardiovascular morbidity and mortality [2]. In addition to elderly age, male gender, inflammation, mineral metabolism abnormalities and diabetes, new potential factors are emerging which help to better understand the pathogenesis of VC in CKD. In the last decade, both new molecular and cellular mechanisms have been investigated in the pathophysiology of secondary hyperparathyroidism and VC in CKD [3–5]. Accordingly, different bone-related proteins are now certified for their capacity of promoting or inhibiting the process of extraskeletal calcification [6, 7]. The pathogenesis of phosphate-induced VC has been investigated in depth [8], and different in vitro studies have demonstrated that high phosphate concentration in growth media causes VC by a specific activation of the core-binding factor α_1 (Cbfa1), an osteoblast-specific gene that regulates the expression of several bone morphogenic proteins [9]. In CKD, the expression of these proteins was also caused by serum from uremic patients with normal serum phosphate [10]. Interestingly, an increased expression of both Cbfa1 and osteopontin has been shown in calcified arteries from CKD patients [11]. Clearly, these data suggest that VC is an active process. The cellular formation of a

bone-like structure in calcified vessel walls indicates that the uremic environment and elevations in serum phosphate levels may be regulating factors. Considering the concentration product of serum calcium and phosphate, physicochemical crystallization would occur continuously if it were not inhibited by specific macromolecules.

The chronic 'nonspecific' microinflammation, a typical condition of CKD, has been investigated as a well-recognized risk factor involved in the pathogenesis of accelerated atherosclerosis and VC. In fact, end-stage renal disease patients with either VC or valvular calcification may have higher serum levels of different markers of inflammation, such as C-reactive protein, tumor necrosis factor α or interleukin 6 [12].

Switching from experimental studies to the clinical setting, it is a well-accepted concept that optimizing therapy to reduce hyperphosphatemia is crucial for minimizing extraskelatal calcification in uremic patients. Recently, sevelamer carbonate, an improved, buffered form of sevelamer hydrochloride, has been studied in patients with CKD not on dialysis [13] and under dialysis treat-

ment [14]. Serum bicarbonate levels decreased with sevelamer hydrochloride, but both sevelamer carbonate and sevelamer hydrochloride demonstrated efficacy in controlling serum phosphorus. Sevelamer carbonate may have advantages over sevelamer hydrochloride in the treatment of hyperphosphatemia in both CKD and hemodialysis patients, where previously bicarbonate levels were shown to be reduced when switching from calcium-based binders to sevelamer hydrochloride [15].

In conclusion, current evidence suggests that bone mineral derangements represent a plausible target for therapy. Indeed, careful evaluation of phosphate binder choice seems to improve survival in hemodialysis patients. Although promising, these results are mainly based on retrospective and observational data, and more randomized clinical trials are needed to confirm these findings in CKD patients. Furthermore, survival data from newer non-calcium- and non-aluminum-containing phosphate binders are awaited to shed further light on this complex syndrome and hopefully ameliorate survival in CKD.

References

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