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Hypocalcemia and cramping in dialysis patients

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The turn of the millennium brought a swing of the pendulum way over to the side of avoiding calcium in every form when treating secondary hyperparathyroidism in the dialysis or chronic kidney disease population. We are perhaps on the side of being overly cautious even when not prescribing calcium containing phosphate binders. This concept was initially based on a cross-sectional study of 39 chronic dialysis patients who underwent electron beam computed tomography to examine the degree of calcification in the coronaries (1). Authors found that 14 of the 39 patients examined had a higher coronary artery calcium (CAC) score. These patients took more calcium containing phosphate binders, had a much higher dialysis vintage (14 versus 4 years; $P < 0.001$), had a higher phosphate level (6.9 vs. 6.3 mg/dL; $P = 0.06$) and a similar serum calcium level (9.5 versus 9.1; $P = 0.25$). Thus they concluded or alluded that calcium containing phoshate binders may be the culprit in soft tissue calcification, including calcification of the coronaries. Since then, a storm of urging withdrawal of calcium containing binders and a restriction of calcium intake by any form has begun. Their theory was further supported by other studies thereafter (2,3). Based on that, scientific bodies issuing guidelines and dialysis providers have instituted protocols and recommendations to restrict calcium containing binders, calcium in the dialysate and calcium in any form. These recommendations have spread to other parts of the world, where some dialysis service providers started to use low, or ultra-low, calcium containing dialysates at 1.25 mmol/L (2.5 mEq/L) for all patients.

Nonetheless, they conveniently ignored the other part of the equation – the supra-physiologic doses of activated vitamin D, its analogous (calcitriol or paricalcitol) and FGF-23, other potential hidden players in this game. It is well-known that calcitriol and its analogues drive excessive absorption of calcium and, ultimately, contributing to soft tissue calcification. On the other hand, some studies have linked FGF-23 to peripheral vascular calcification and/or CAC score (4,5). Not surprisingly, in attempts to regain some balance, just recently, KDIGO CKD-MBD 2017 guidelines suggested not to routinely use calcitriol and vitamin D analogue in CKD G3a-5 patients (6).

Implication for health policy/practice/research/medical education

Further randomized controlled studies involving FGF-23, vitamin D and its analogues are still needed for an affirmative answer whether to continue with a low calcium bath/Ca^{2+} deprivation protocol for renal patients. We believe, in the current era of exponential increase in knowledge funds and discoveries – thanks to the tremendous amount of research being conducted – patience in changing health policies/guidelines is sometimes favorable to frequent changes.

Moving forwards in viewing this matter from a deeper and different perspective, as a consequence of using ultra-low calcium dialysate, other types of hypocalcemia complications have been noted (7). Particular concern is this phenomenon during large-volume on-line hemodiafiltration (8), which infers with the net initial high bicarbonate transfer and further drop of ionized calcium (9). Currently in the era of high-flux dialyzers, even what is considered a "conventional" hemodialysis enables a significant hemofiltration process via "back-filtration" process (4-8 L per during a 4-hour session) (8,10). Some large-volume dialysis provider network perform regular, monthly or quarterly fluid status assessment via bio-impedance spectroscopy to facilitate reaching clinical euvolemia, customarily called "dry weight" (11,12). However, during their dialysis they develop muscle cramping towards the end of their treatment sessions, most likely not due to volume depletion but hypocalcaemia (9, 13). This has been confirmed in clinical practice by checking the ionized calcium level (the measurement readily available at the point of care in many countries) and by the intravenous administration of calcium gluconate which immediately abates the muscle cramping. In fact, the latter is considered a therapeutic and diagnostic trial

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for abolishing cramps due to low serum ionized calcium levels. Although this muscle cramping is only a matter of discomfort, intradialytic ionized hypocalcemia is a more serious condition. The corrected QT interval on the EKG tracing is often prolonged in hypocalcemic patients (14, 15) and prolonged QT interval is a known cardiac risk factor for sudden death (16,17), potentially explaining the paradox increased risk of dying after renal dialysis (18-20).

The pendulum has swung and it may have swung too far! We became so cautious and fearful of hypercalcemia that nowadays we may be part of inducing most of our patient's hypocalcemia and potentially causing other serious complications. The question is whether we have done any good with this or we should have just waited the storm out? The situation is similar to the hurricane warning, sometimes it is wiser not to go anywhere and just to wait and see.

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