Calcium, Calcium Regulatory Hormones, and Calcimimetics: Impact on Cardiovascular Mortality

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Calcemia is a risk factor for cardiovascular (CV) events in dialyzed patients. The relation between serum calcium and cardiovascular events is continuous and linear. Calcium plays a potent role in the genesis of cardiovascular dysfunction, particularly by promoting vascular calcification. Parathyroid hormone (PTH) also is associated with increased CV risk in both primary and secondary hyperparathyroidism. There is a nonlinear relationship between PTH and CV risk; both high and low PTH concentrations increase CV risk. The CV risk profile (BP, dyslipidemia) is strikingly ameliorated by the administration of calcimimetics. Apart from lowering PTH, whether calcimimetics have intrinsic effects on CV risk profile is unknown.

Correlations between Survival on Dialysis and Calcemia or Calcium Regulatory Hormones

It has been known for some time that cardiovascular (CV) morbidity and mortality are increased dramatically in patients who are on maintenance hemodialysis (1,2). For a long time, it has not been appreciated that concentrations of parathyroid hormone (PTH) as well as of calcium and phosphate have an impact on patient survival. In 1998, Block et al. (3) reported a progressive increase in mortality when the predialytic phosphate concentration exceeded 6.5 mg/dl. Subsequent analyses showed that this was due to an increase in coronary mortality (4). More recently, it has been documented that high phosphate concentrations promote vascular calcification (5–7) but also other cardiovascular abnormalities (8).

The impact of calcium on survival has been less obvious. This is because interactions between calcium phosphate and PTH are complex (9,10). Block et al. (10) observed a continuous linear increase of CV mortality with increasing predialytic concentrations of calcium (corrected for protein). One potential explanation for the strikingly adverse effect of calcemia is potentially the observation of Ghiacelli and colleagues (11,12) that calcium potentiates the ability of phosphate to promote vascular calcification (5). However, it is also important to consider the adverse effects of hypercalcemia and hypocalcemia on CV outcome.

Calcimimetics and CV Risk Profile

A major breakthrough in the management of the deranged calcium phosphate metabolism of dialysis patients was achieved recently with the introduction of calcimimetics (24). These are the first agents that lower PTH without increasing the concentrations of serum calcium and phosphate. Calcimimetics act as allosteric modulators of the calcium-sensing receptor (25,26). This receptor is ubiquitously expressed in almost all cells. The question arose whether administration of calcimimetics has (potentially adverse) effects beyond lowering of PTH. To address this issue, Ogata et al. (27) performed in subtotally nephrectomized rats an experiment that proved that the calcimimetic NPS-R 568 lowered BP, reversed dyslipidemia, attenuated progression (reduction of albuminuria, less glomerulosclerosis), and improved cardiac morphology (capillary density, fibrosis). The magnitude of these effects was compa-
rable to that seen with parathyroidectomy, illustrating the concept of Massry that PTH is a uremic toxin (21). It is currently unsettled whether all of these effects of calci-mimetics on the CV risk profile are due to lowering PTH or calci-mimetics have direct effects on target structures such as vessels or adipocytes. Vessels (28) as well as adipocytes (29) express calcium-sensing receptors. Calcium modulates the function of vessels, i.e., reduces luminal width followed by vasodilation (28), and the function of preadipocytes, i.e., sup-presses expression of differentiation markers such as peroxisome proliferator–activated receptor γ, diminishes fat storage, etc. (29). In this context, our recent finding that calci-mimetics influence the BP profile, as measured by telemetry, is of con-siderable interest (30).

An unknown factor is the action of vitamin D on CV risk. The issue is of clinical relevance, because it is likely that despite new approaches to patient management, including calci-mimetics, the need for administration of vitamin D or its analogues, presumably in lower doses, will persist. The issue is very complex (31). On the one hand, adequate vitamin D is essential for optimal vascular function (32). Absence of vitamin D as in vitamin D receptor knockout mice causes hypertension and high renin expression (33), and, conversely, 1,25(OH)2D3 amplifies expression of ANP type A receptors, which should be beneficial for CV risk (34). On the other hand, vitamin D, admittedly at toxic and hypercalcemic doses, was prothroph-genic in animal models (35); more convincingly, it also exacer-bates intimal hyperplasia after carotid balloon injury (36). Fur-thermore, it stimulated processes that are involved in aterogenesis, such as proliferation and migration of vascular smooth muscle cells (37). It is interesting that a retrospective observational study suggested recently that mortality, including CV mortality, was less in hemodialyzed patients who were treated with paricalcitol as compared with calcitriol (38). It has been suggested that paricalcitol does not act as a classical agonist but rather as a vitamin D receptor modulator. Definite proof for this concept and replication of the finding in a controlled prospective study are not yet available, however. This whole area is in dire need of further investigation.

It follows from the above that calcium and calcium regula-tory hormones are important CV risk factors and contribute to the diminished survival of uremic patients who are on mainte-nance hemodialysis. It remains to be seen whether calci-mimetics by controlling hyperparathyroidism without provoking an increase in calcemia and phosphatemia will improve sur-vival of dialyzed patients.

References
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