Pro/Con Debate

Calcium balance in haemodialysis—do not lower the dialysate calcium concentration too much (con part)

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Abstract
The debate on the most adequate dialysate calcium concentration for intermittent haemodialysis therapy is ongoing. There is probably no one optimal concentration. In general, one would like to maintain a neutral calcium balance in adult haemodialysis patients. However, a slightly negative balance may be preferable to avoid soft-tissue calcium accumulation in face of net calcium loss from the bone with ageing. The problem with measurements of calcium balance is that they are generally imprecise, as are estimations of total body calcium and its distribution in various compartments, unless done with labour-intensive methods and great care. The choice of the dialysate calcium will depend on several factors, including parathyroid and vitamin D status, type and severity of concomitant bone disease, presence or absence of arterial calcification, dietary habits, drug treatment and dialysis modality. Ideally the dialysate calcium would be adapted to each patient’s needs. This is not feasible, however, in most dialysis settings and neither is it cost-effective. From a practical point of view, a relatively high dialysate calcium concentration in the range of 1.50–1.75 mmol/L (3.0–3.5 mEq/L) should probably be preferred in haemodialysis patients with high serum PTH levels who are not prescribed calcium-based phosphate binders or high doses of active vitamin D sterols, and in those who are receiving a calcimimetic. In those who are treated with high doses of calcium-based binders and/or active vitamin D derivatives or who have a very low serum PTH level, the optimal dialysate calcium concentration is probably lower, in the range of 1.25–1.50 mmol/L (2.50–3.0 mEq/L). In the present pro/con debate about the optimal dialysate calcium concentration used for the haemodialysis session, we have accepted to defend the viewpoint that a low calcium concentration may do more harm than benefit in many patients. This viewpoint is opposite to that taken by Gotch [1]. He argues that since calcitriol and other active vitamin D derivatives have become available virtually all haemodialysis patients are in positive calcium balance. We would like to take issue with this statement and warn against the indiscriminate use of a low calcium dialysate in all patients receiving haemodialysis therapy.

Keywords: calcium balance; CKD; dialysate calcium; haemodialysis; parathyroid hormone; phosphate binders; vitamin D

Calcium balance in haemodialysis patients

In patients receiving intermittent haemodialysis treatment, calcium balance depends on a variety of entry and exit pathways. It therefore differs from those of healthy persons. Although it is controlled in part by the well-known homeostatic mechanisms involved in the regulation of calcium metabolism under physiological conditions, these mechanisms are disturbed in the presence of chronic kidney disease (CKD). The capacity to excrete calcium in the urine is seriously compromised in advanced stages of CKD. It gets entirely lost in anuric patients. Last but not least, the dialysis procedure introduces an additional calcium entry and exit mechanism.

In chronic dialysis patients, the calcium balance thus is the result of net calcium absorption from the gut, calcium excretion via residual urinary output, calcium loss through the skin in case of transpiration and net calcium transfer during each dialysis session. The main factors involved in intestinal calcium absorption are the amount of dietary calcium ingested, other food components interfering with its absorption (such as phosphate and oxalate), the intake of calcium-containing phosphate binders, the vitamin D status and the administration of active vitamin D derivatives. Although active [2] and fractional [3] intestinal calcium absorptions are decreased in uremic patients compared with healthy volunteers the ingestion of supraphysiological amounts of calcium can lead to calcium overload because passive transintestinal transfer is normal [2]. In chronic haemodialysis patients, excessive calcium uptake from the gastrointestinal tract cannot be eliminated via the kidneys since residual renal function is generally low or nil. The amount of calcium lost during transpiration may amount to as much as 103 mg/day [4,5] but this remains a matter of debate [6]. The net calcium balance during a dialysis session depends on the diffusion gradient between the
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ultrafilterable calcium concentration in the blood and that of the dialysis fluid, the dialysance of calcium, the ultrafiltration rate and the duration of the session.

**Distribution of calcium in the healthy organism and in patients with CKD**

The distribution of calcium in the organism is extremely complex, even under physiological conditions [7]. More than 99% of calcium is present in bound form and located in the bone, which functions as a calcium bank. The remainder is distributed within the intracellular and extracellular fluid space, either in bound or free form. Free calcium is either in diffusible (ultrafilterable) non-ionized form or in ionized form ($Ca^{2+}$). There is a steep concentration gradient between $Ca^{2+}$ in the intracytoplasmic and extracellular milieu. In advanced stages of CKD, deposition of calcium together with phosphate or other anions can also occur in soft tissues where normally there is none. In dialysis patients, this is a frequent event, as demonstrated by the presence of vascular, valvular and other extraosseous calcifications. These are generally made of either amorphous deposits containing calcium, phosphate and magnesium or of hydroxyapatite crystals [8]. However, other calcium containing deposits such as oxalate crystals and magnesium-containing whitlockite can also be observed [9,10]. Soft tissues therefore potentially constitute a fifth compartment of the calcium distribution in the body, in addition to the four major classical compartments which are the gut, the intravascular/extracellular space, the kidney and last but not least the bone [11]. Strictly speaking, there is an additional intracellular calcium compartment which itself can be subdivided into the cytoplasmic compartment and subcellular compartments made of organelles such as the mitochondria and the cytoplasmic reticulum. The five-compartment model can be transformed to a four-compartment model in anephric haemodialysis patients (and tentatively also in all anuric patients), and further reduced to a three-compartment model in those with adynamic bone disease, as shown, as proposed by Braun (Figure 1) [12].

**Net calcium balance versus complex calcium distribution**

When discussing issues related to calcium balance, one has to take into account the complexity of the distribution of calcium in the different body compartments and its fluxes from one compartment to the other, all the more when the distribution is abnormal in clinical conditions such as CKD, with major disturbances being observed in patients with end-stage kidney disease (ESKD). In adult haemodialysis patients, the consideration of overall calcium balance alone, that is net input into the patient minus net loss from the patient, is not useful from a clinical point of view, be it based on simple estimations or complex kinetic models. Here are some practical examples to make the point more clear.

A positive calcium balance is beneficial after parathyroidectomy in a haemodialysis patient with severe secondary hyperparathyroidism who recovers from osteitis fibrosa, where bone formation is greater than bone resorption and thus new, mostly cancellous bone is formed and abnormal bone structure is partially repaired.

A positive calcium balance may be harmful in a haemodialysis patient with adynamic bone disease in whom the calcium cannot be used to form new bone or make bone more resistant to fracture, but in whom it is deviated to pathological deposition in soft tissues.

Of note, even a neutral calcium balance may be harmful in an adult haemodialysis patient with high turnover bone disease in whom bone resorption prevails over bone formation. Such a patient has an obligatory net skeletal loss of calcium, phosphate and magnesium that may greatly exceed the physiological loss with age. The excessively released ions cannot be eliminated from the body in the absence of functioning kidneys. They are therefore deposited in extraosseous tissues.

**The dilemma of estimating calcium balance in haemodialysis patients**

Estimates of calcium transfer during a haemodialysis session from the patient to the dialysis fluid and vice versa may be relatively precise. However, it is practically impossible to obtain accurate information on net intestinal calcium absorption in such patients, not to speak of...
calcium losses with sweat. Balance studies involving precise measurements of oral intake and faecal as well as urinary excretion of calcium are very difficult to perform. Only a few have been conducted in patients with CKD during the past 50 years. Investigations using single or double calcium isotope techniques to estimate intestinal absorption are time consuming, potentially harmful (unless done with natural isotopes) and costly. Estimates based on changes in the serum calcium concentration or urinary calcium excretion in response to known amounts of calcium ingested are unreliable, particularly so in patients with CKD [12,13]. We are therefore left with approximations and extrapolations based on literature reports from the 1970s and 1980s, with highly variable findings depending on the exploration technique used, the metabolic, endocrine and nutritional conditions of the patients under study and the treatments received.

Potentially beneficial effects of a low calcium dialysate

In haemodialysis patients with a positive calcium balance lowering the dialysate calcium concentration may be useful to achieve a neutral or even negative balance. However, if the calcium excess is secondary to an increase in intestinal calcium absorption, for instance due to excessive calcium intake or the administration of high doses of vitamin D sterols, it would appear more appropriate to take measures aimed at reducing the enhanced calcium uptake from the gut first.

In the presence of adynamic bone disease and low serum parathyroid hormone (PTH) levels, the use of a low calcium dialysate has been shown to increase circulating PTH and bone-specific alkaline phosphatase in haemodialysis patients [14,15] and to increase both serum PTH and bone formation rate in patients receiving peritoneal dialysis treatment [16].

Potentially harmful effects of a low calcium dialysate

Excessive lowering of serum calcium during the haemodialysis session by a low dialysate calcium concentration may be associated with more frequent episodes of hypotension [17,18] and cardiac rhythm disturbances. Probably, the most life-threatening episodes are ventricular arrhythmias in association with concomitant hypokalaemia [19].

A low dialysate calcium concentration has been shown to lead to an increase in serum PTH [20,21]. This should be avoided in dialysis patients with established hyperparathyroidism and high turnover bone disease in whom a negative calcium balance may be worsened further [21]. The control of secondary hyperparathyroidism in patients treated with low dialysate calcium (1.25 mmol/L) may require higher doses of paricalcitol than when treated with higher dialysate calcium concentrations (1.50–1.75 mmol/L) [22].

In patients with long daily or nocturnal haemodialysis sessions, a low dialysate calcium concentration may lead to excessive bone mineral loss and therefore a relatively high concentration may be necessary to prevent osteopenia [23].

Potentially beneficial effects of a high calcium dialysate

It has long been known that higher dialysate calcium, compared with a low, dialysate calcium concentration is associated with better haemodynamic stability, that is less frequent hypotensive episodes and better cardiac contractility indices during the haemodialysis session [17,24]. This is particularly true in patients with compromised cardiac function [18]. High bicarbonate together with a high calcium concentration of the dialysate may even further improve the haemodynamic pattern during the haemodialysis session [25].

In haemodialysis patients with secondary hyperparathyroidism, a dialysate calcium concentration of 1.75 mmol/L results in better control of parathyroid overfunction and high turnover bone disease than with lower dialysate calcium concentrations [26–28]. The introduction of cinacalcet for the treatment of such patients, which decreases not only serum PTH but also serum calcium and phosphorus [29], requires the dialysate calcium concentration to be higher than in patients treated with drugs which increase serum calcium and/or phosphorus. When dialysis patients with parathyroid overfunction receive cinacalcet therapy, a high dialysate calcium concentration may allow the control of serum PTH levels with lower doses of the calcimimetic than when using a low dialysate calcium concentration [30].

In an uncontrolled study in a cohort of 387 haemodialysis patients, long-term survival was excellent with the exclusive use of high dialysate calcium concentrations (either 1.5 or 1.75 mmol/L), that is 92% after the first year, 82% after 2 years and 55% after 5 years [31].

Potentially harmful effects of a high calcium dialysate

Although control of secondary hyperparathyroidism is effective with a high dialysate calcium concentration (1.75 mmol/L), dialysis patients are at increased risk of developing oversuppression of PTH and adynamic bone disease, hypercalcaemia and soft-tissue calcification [32]. This is particularly true for those patients who are receiving oral calcium supplements, including calcium-containing phosphate binders and active vitamin D derivatives that tend to enhance intestinal calcium absorption and to induce hypercalcaemia.

Conclusion

The optimal calcium concentration of the dialysis fluid must be a compromise between the need to guarantee cardiovascular stability during the haemodialysis session and the goal to maintain normal bone turnover and mineralization in order to avoid bone pain and fractures.
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