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Controversy of Dialysate Calcium Concentration

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DR. BLOCK: My name is Dr. Geoffrey Block. I'm the Director of Clinical Research at Denver Nephrology. Joining me today are Dr. David Bushinsky, Professor of Medicine at the University of Rochester Medical Center; Dr. Pieter Evenepoel, Professor of Medicine at the Department of Immunology in Belgium; and Dr. Allan Collins, Professor of Medicine at the University of Minnesota, Director of the Chronic Disease Research Group, and the Executive Director of the Peer Kidney Care Initiative. I'm really grateful to all three of you for being here and having this discussion today.

I think that this will be an interesting discussion. It's an interesting topic, and all three of you are experts in this area. I'm looking forward to seeing what you think. Pieter and I have had discussions along this line, in the not too distant past, through our participation in the Kidney Disease Improving Global Outcomes (KDIGO) workgroup.

The topic that we're discussing is the controversy of dialysate calcium concentration. Let me frame the discussion from my perspective, which is what I think is leading to this so-called controversy, if there is one, is the fact that it's been recommended recently—or at least acknowledged—that most dialysis patients are likely to be in positive calcium balance when they're given active vitamin D therapy and particularly when they're given calcium-containing phosphate binders. In an effort to try to theoretically address this positive calcium balance issue, a number of people have suggested over the last few years that we reduce the dialysate calcium concentration, and by doing so, would potentially allow for a neutral calcium balance because we're administering so much calcium orally, that we might be able to achieve a neutral balance by lowering calcium or increasing calcium lost during the dialysis procedure.

I think all four of us know that this is not as straightforward as it sounds. I'd like to start with that particular concept, which is using dialysate calcium to allow us to achieve a so-called neutral calcium balance. David, tell me, what are we missing when it seems like a reasonable—on-the-surface—proposal to adjust calcium dialysate to allow for this balance issue, but not sure that it actually is quite so simple? What do you think?

DR. BUSHINSKY: Dr. Block, that's an interesting concept. Let's go back to 2010. We began to think about this and actually wrote in the *Clinical Journal of the American Society of Nephrology*[1] and then *Nephrology, Dialysis, Transplantation*[2] about extracellular fluid calcium content in dialysis patients. We were concentrating on what you mentioned, the calcium intake. We determined through review of a lot of studies and mathematical modeling that without vitamin D, people could safely take in

ABSTRACT

The discussion focused primarily on: 1) Clinical concerns regarding fluctuating calcium levels in dialysis patients; 2) The risks associated with lowering dialysate calcium below 1.25 mmol/L in an effort to reduce positive calcium balance or mitigate calcium intake from calcium-based phosphate binders; 3) Caveats and concerns over using high calcium dialysates; and 4) Clinical consequences of using low or high calcium dialysates. [Published online ahead of print May 20, 2016.] *Med Roundtable Gen Med Ed.* 2016 May 20.

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about a gram and a half of elemental calcium per day, and with vitamin D, about a gram of elemental calcium per day. Any more calcium than that, they would be in positive calcium balance. This was based on the thought that if you absorb calcium and you have essentially no renal function, there's no way to excrete that calcium. Once the bone calcium needs were met, that calcium would accumulate in the extracellular fluid, and since the level of serum calcium couldn't continue to rise, that calcium would be deposited in soft tissues including the vasculature.

Along with the thought of diet calcium, you bring up the great point of dialysate calcium, and it's the same concept. If you establish a gradient of calcium from the dialysate into the patient, you will achieve a positive calcium balance, and the calcium will deposit in the soft tissues. The thought of using a low calcium dialysate to cause an efflux of calcium from the patient to the dialysate, which would allow the use of oral calcium, especially with activated vitamin D is, on the surface—as you say—reasonable. However, calcium is not urea. Calcium is not a waste product. It's an active signaling molecule. If you dialyze people on a low calcium bath, their arterial blood ionized calcium will fall. Their parathyroid hormone (PTH) will rise, and the low calcium will induce cardiac instability. That has been amply shown in several studies. We, years ago, demonstrated that dialyzing against a low calcium bath reduced left ventricular (LV) function.[3,4]

Patients' cardiac output went down. Patients' blood pressures went down. Dialyzing against a low calcium bath is not without the hazards of hypotension, reduced LV rejection fraction and, as Jack Coburn showed years ago,[5] increased PTH. I could expand upon this, but perhaps it's time to pass this on to someone else.

DR. BLOCK: That's fantastic, David. Thank you. It is pretty remarkable, isn't it, that the whole concept of reducing dialysate calcium—honestly, from what I can tell—is meant to provide this theoretical room to give more and more calcium orally? The irony being, as you just said, that by using a low dialysate calcium, you will end up increasing PTH, and potentially increasing phosphate—and we can talk about one of the clinical studies that actually showed that—but if you increase phosphate and you increase PTH, you end up having to provide even more drug therapy. You're actually making a cycle of events worse, or at least theoretically worse.

Allan, what are your thoughts on this whole concept? You've been doing dialysis and running a dialysis center for a very long time. What are your thoughts on trying to manipulate the dialysate calcium for the purpose of achieving a neutral calcium balance?

DR. COLLINS: Let me bring in this perspective that you've heard me talk about. What does any of this stuff have to do with sudden death that's going on with the dialysis population, the largest cause of cardiac death? A number of years ago, David and Geoff and Pieter, a number of you heard me when I was running the United States Renal Data System (USRDS) articulate this issue that arrhythmic complications, as you approach the end of a dialysis procedure, increased. Anybody who sat in a dialysis unit could actually see this, either by asking the nurses how many extra systoles they had at the end of the run, but if you look at the electrocardiograms at the end of the run—those of us who did a lot of research—you'd find that the QT intervals tend to lengthen out during the run.

I come at it from the fact that, when David articulates this issue of what the low calcium bath is doing toward the heart, that by the end of the run, you sort of have a perfect storm that's going on relative to electrolyte abnormalities. The ionized calcium is falling. The bicarbonate is rising, so that's also driving the ionized calcium down. The magnesium is falling because we dialyze on a very low magnesium bath. The QT interval increases. The beta-blockers are dialyzed off. The angiotensin-converting enzymes are dialyzed off. Everything that protects the patient from arrhythmic complications actually gets worse by the time you get to the end of the run. Dialyzing on calcium baths, even if the ionized calcium was equal to the blood calcium, the fact that we push the bicarbonate up means that we drive the ionized calcium down, so that sudden death may actually be exacerbated by low calcium bath. That's my concern about that.

DR. BUSHINSKY: Didn't Pun show in a review of the DaVita database[6] that, yes, a low potassium bath was associated with increased cardiovascular mortality, but so was a low calcium bath?

DR. COLLINS: Yes. They both potentiate each other. So, the low potassium, the low calcium, the low magnesium, and the high bicarbonate all are impacting the QT interval and are all arrhythmogenic by their nature.

DR. BLOCK: Let me ask a question to both of you before we hear Pieter's thoughts. We know that with potassium, as both of you brought up, that the gradient between the patient and the dialysate is of really utmost importance. It's not just what is the potassium bath, it's what's the gradient in either direction, and I guess what I'm hearing is that—it's not exactly the same, but similar to the concept here—the gradient between the patient and the bath is going to be ultimately quite important here as well.

DR. COLLINS: Yes.

DR. BUSHINSKY: Yes.

DR. COLLINS: David, if you really look at the sweet spot of where the potassium is supposed to be, whether it's from Kam Kalantar's papers or a few of the other papers, either in dialysis populations or nondialysis populations, really, you'd like the potassiums to be between 4 mg/dL and 5 mg/dL.[7-9]

DR. BUSHINSKY: Absolutely, Allan. We, as nephrologists, are always worried about the high potassium, but our cardiology colleagues impress upon us that a low potassium is also arrhythmogenic and associated with increased mortality, so this perfect storm that you speak of, of a low calcium, a low potassium, a low magnesium in the presence of a high bicarbonate is potentially, incredibly arrhythmogenic and may well explain much of the mortality at the end of those dialysis treatments.

> ***"I completely agree that we should avoid this kind of storm during the dialysis session. There are so many changes in the different ions that could trigger some arrhythmia. I completely agree that we should avoid important gradients, whether the ion is calcium or potassium."***
>
> **Pieter Evenepoel**

DR. EVENEPOEL: I completely agree that we should avoid this kind of storm during the dialysis session. There are so many changes in the different ions that could trigger some arrhythmia. I completely agree that we should avoid important gradients, whether the ion is calcium or potassium. Now we're discussing calcium. I think we surely shouldn't use the dialysis time just to get rid of the calcium that we build in the time before the dialysis. That's one point. Another point, the data we're certainly missing so far are, of course, what is the calcium balance in dialysis patients, and especially what is the fractional gastrointestinal absorption in renal failure patients? Most estimates with regard to the latter are derived from calcium isotope tracer studies which, it should be emphasized, do have important inherent limitations.[10] According to these isotope tracer studies, the fractional intestinal calcium absorption rates in dialysis patients was estimated at 25%. Tracer techniques may overestimate real calcium absorption substantially since they do not account for impaired calcium release from the food (digestion and solubilization), which may be especially relevant in pathological conditions such as chronic kidney disease (CKD). Again, I would point to the model being put forward by David in his paper where he modeled the calcium balance according to calcium intake and according to vitamin D intake.[1] This is based on the assumption of a fractional gastrointestinal calcium absorption of 25%, which I just mentioned could be an overestimation. If it were truly less then, again, calcium balance wouldn't be that positive, even in the intradialytic time period. We should, again, be very careful in stating that the calcium balance is for sure positive in dialysis patients on 1,25D therapy when they're consuming, let's say, one gram of elemental calcium. I think this is certainly something that should be put in with a question mark.

DR. BUSHINSKY: Absolutely. If I might interject, there are now several studies, one by David Spiegel,[11] and a second by Katie Hill,[12] and they both show basically the same thing. David did a formal calcium balance study in six patients with CKD and six healthy controls, and compared those on an 800 mg per day calcium diet and those on a 2000 mg per day calcium diet. Those on the lower calcium diet were in neutral calcium balance. These are CKD patients, so they have some renal function, and those on a high calcium, or 2 g calcium intake, were in positive calcium balance. Katie Hill demonstrated essentially the same results in another study. She took eight patients with CKD, put them on about 950 mg of calcium, and supplemented 500 mg of calcium carbonate or placebo three times per day. Thus the patients received about 950 mg versus about 2450 mg of calcium a day. Again, on the lower calcium diet, the patients were in neutral calcium balance. On the higher calcium intake, the addition of 500 mg of calcium three times per day, led to a marked increase in calcium balance of about 500 mg per day, suggesting the calcium absorption was about 33%, even higher than the 20% that Jack Coburn found and that we used in our mathematical modeling. If anything, Katie Hill found more calcium was absorbed, approximately 33%, with these stage 3 and 4 CKD patients than we normally assume.

DR. BLOCK: There are a couple of interesting issues here. One is, we don't really know with modern patients what the calcium balance is

because we don't really know the fractional absorption in the setting of CKD with or without vitamin D therapy. The second issue is, David, that you so beautifully, I thought, wrote in both of your papers,[1,2] that regardless of balance, the kinetics of where calcium is moving with regard to extracellular fluid calcium concentration, because ionized calcium is so tightly regulated, that the kinetics of where the calcium is moving is probably equally as important as whether patients are in neutral, negative, or positive calcium balance. To take a very simplistic approach to just trying to achieve so-called neutral balance may tell you nothing about where that calcium is actually living within the individual.

DR. BUSHINSKY: Thank you, Geoff. Let me just briefly comment that the typical physiologic environment of our patients, the metabolic acidosis, the administration of 1,25 D or analogs, and their high PTH all move calcium from the bone, where we want it to be, to the soft tissues, where we don't want it to be.[1,2] You're absolutely right. In our CKD and dialysis patients, not only might they be in positive calcium balance, but the calcium is maldistributed. More is in the soft tissues, and less is in the bone.

DR. BLOCK: I think we're all aware of—and I think pretty impressed by—the work of some of the basic scientists, like Catherine Shanahan and Giachelli,[13] who have shown that intracellular calcium content of patients with CKD, even pediatric patients with CKD, is staggering. Long before we can see or detect the calcium accumulation in soft tissue, the intracellular calcium content is accumulating tremendously.

I want to move for a second over to you, Allan. Given your incredible experience running the USRDS and now with the Kidney Peer Initiative, I would like to hear your comments on this analysis by Steve Brunelli,[14] who actually looked at it in a retrospective way. Because this notion of low dialysate calcium gathered some momentum, there was a number of facilities within the large dialysis organizations that actually switched the majority of their patients in their facility to a low dialysate calcium. I was really impressed with this retrospective analysis, of looking at outcomes in facilities that switched to a low dialysate calcium compared to those who stayed on what is generally recommended, the 1.25 mmol/L calcium bath, because it actually supports exactly what you and David and Pieter were just saying with regard to what happened with arrhythmogenicity. What are your thoughts on that analysis?

> ***"...every time you remove a liter of ultra filtrate, you're removing the calcium with that liter of ultrafiltrate. We built that into the model, and we routinely ultrafilter 3L of fluid during each dialysis session. That's a fair amount of calcium that we're removing. If you couple that with a low calcium dialysate, you're removing a substantial amount of calcium from the body..."***
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> **David Allen Bushinsky**

DR. COLLINS: What I liked about what Steve did is he looked at the causal path to say all right, if this calcium has a multiplier effect by just what we were talking about, through the electrolyte abnormalities that are going to occur by the end of the run—and we're discounting the bone and mineral issues here—but if it really does have this causal path, then not only should we see all cause mortality, we should see very specific types of morbidity from these arrhythmic events. What did we find? We found exactly that. I said, "Gee, that really sort of gives you a wake-up call that this fooling around with the calcium and the bath has to be put in the context of, what are the overall things that are going on that create the major morbidity and mortality?" Of the hospitalization events, atrial fibrillation is probably number three now as a cause of cardiac hospitalization, beyond heart failure and acute myocardial infarctions, we've got atrial fibrillation that occurs. These QT prolonging electrolytes, low electrolytes to prolong the QT interval, creates this conduction, accelerated conduction abnormalities in the heart as opposed to, we're so used to the high potassium side of the equation, which actually moves to asystole. All these arrhythmic problems that we actually have may be traceable to this combination of too aggressive use of low calcium.

One other element I'd like you to consider—and David, you'd probably want to comment on this as well—is the amount of ultrafiltration that's going on during the dialysis treatments and the amount of solute drag that's occurring with the Donnan effect is also going to affect how much ionized calcium is coming across the membrane. With the European

dialysis population—where 30% of them are now on hemodiafiltration (HDF)—where there's a lot of flux that's going on across the dialyzer, 25 years ago, when we were doing hemofiltration quite a bit, we got into pretty substantial calcium balance problems when we were using convective transport to cross the membrane. Obviously, ultrafiltration itself is a convective transport system. Do you want to comment on that, David, on how that plays a role in the net calcium balance here?

DR. BUSHINSKY: Absolutely, Allan. When we did our analysis in 2010, we recognized—as you so beautifully said—that every time you remove a liter of ultrafiltrate, you're removing the calcium with that liter of ultrafiltrate.[1] We built that into the model, and we routinely ultrafilter 3L of fluid during each dialysis session. That's a fair amount of calcium that we're removing. If you couple that with a low calcium dialysate, you're removing a substantial amount of calcium from the body, and this calcium is a signaling molecule. You can't look at calcium as, for example, you look at urea, where, at the end of the week, you want the balance to be neutral. You can't have these large swings of blood calcium that, if it's low, will stimulate PTH and arrhythmias and if it's high, it will suppress PTH and also stimulate arrhythmias. You have to maintain a signaling molecule relatively constant throughout the week.

DR. BLOCK: Pieter, that's a perfect segue to you because I think HDF is quite a bit more common in Europe. What are your thoughts on this since, as David said, we can't make sure calcium transfer and mass calcium over the course of a week are neutral. What do you think of that from a European perspective?

DR. EVENEPOEL: Of course, the European perspective is that HDF is much more common than in the US with a penetrance of about 40% if I'm correct. I completely agree with the point that calcium can be exchanged not only by diffusion but also by convective transport. Studies evaluating calcium balances during HDF are, to the best of my knowledge, not in existence, but you can imagine that net losses may be substantial when using a low calcium dialysate in the setting of predilution hemodiafiltration with convection volumes exceeding 20 L. It's something certainly that is a lack, at least in my opinion, of what's really going on with regard to calcium balance or even just looking at calcium levels, ionized calcium levels in HDF patients as compared with hemodialysis (HD) patients, but surely that's something that should be investigated into more depth. I completely agree this is something that should not be neglected, the amount of calcium being lost just by means of convective transport. I don't think there are any data that are really giving us some insight in this topic.

> ***"The other issue is with trying to infuse calcium with the dialysate when you've got hypocalcemia induced by, let's say cinacalcet treatment. The challenges, as you load the patient during the dialysis run with ionized calcium, it's going to be a pretty potent PTH calcium sensor stimulator to suppress the PTH even further. We're all trying to sort of balance out how to get them through these low calcium periods without disrupting and causing too many other collateral issues that are going on."***
>
> **Allan J. Collins**

DR. COLLINS: You're right. I'm not sure that I've heard much from our European colleagues with this HDF. What exact calcium bath is being used?

DR. EVENEPOEL: It's the same one we use in HD. There's never been an important point that we should increase the calcium dialysate bath when we switch a patient from HD to HDF. It's certainly something not in the guidelines that we use in order to avoid the negative calcium balance during HDF. The typical points are there. It's irrational to increase calcium in the dialysate when you switch to HDF, but again, there are no—at least to the best of my knowledge—data to support this.

DR. BUSHINSKY: We know, based on older studies—they're 20 years old now—where Susan Hou, among three or four other investigators, actually looked at how much calcium was coming out in the dialysate.[15] They collected all and measured all of the dialysate. They found that a 1.25 mmol/L bath resulted in relatively neutral calcium balance

during the conventional HD treatment, 1.75 caused calcium influx into the patient, and 0.75 caused calcium efflux from the patient. That doesn't surprise any of us, but there is absolutely a need for new studies of this important point.

DR. BLOCK: Let me make one quick comment, and then I want to introduce two things that we can end with that I think are really important. The first is, I want to summarize, Allan, what you said about Steve Brunelli's work, because I think it's so interesting. As we've all just been saying for 25 minutes, there's so much we don't know right now about, not only what the calcium flux actually is, but how the kinetics of the calcium movement affect cardiac function during and after the procedure, and I find it incredibly supportive that Steve's work showed that the facilities that switched to a predominantly low calcium bath, the two things that stand out in addition to hypocalcemia are in fact nearly doubling of the risk of atrial fibrillation and heart failure. The two things that, when David introduced this conversation today said, it decreases LV function and, as you pointed out, it increased arrhythmogenicity along with all of the other things that are happening to the patient. There's no question that, particularly as the patient moves from nondialysis to dialysis and we introduce the dialysis procedure itself, we create events. I think that's been pretty clearly shown. The first several months of dialysis, we have this incredible increase in the events. I think we have to be concerned about the relationship between lowering dialysate calcium and making people have these events that are worse.

The two final things—I think we're generally in agreement; there are some substantial risks to low dialysate calcium. On the other hand, there are some excellent papers that have recently come out showing there's substantial risk to high dialysate calcium as well.[16-18] I don't think it's prudent to ignore that aspect either. Particularly in the context of calcimimetics being a therapy that didn't exist 15 or 20 years ago, and that are now reasonably widespread. Let's close, David, with your thoughts on both of those concepts. What have we now learned about high dialysate calcium, either de novo, or in response to a calcimimetic-induced lower serum calcium, and its potential effects?

> ***"...all of us agree that we should have some serious reservations about using low dialysate calcium concentration as a method to achieve neutral calcium balance. Similarly, we have reservations about the use of high dialysate calcium concentration, and I think, at the end of the day, the KDIGO recommendations...suggest that a 1.25 calcium dialysate is, in fact, a very reasonable approach to balance this issue of kinetics and calcium balance."***
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> **Geoffrey A. Block**

DR. BUSHINSKY: Yes, Geoff. As you mentioned, two important papers just came out. Merle published a paper saying that a decrease in PTH from a high to a normal value induced by a high dialysate calcium was a strong independent predictor of cardiovascular mortality 12 to 24 months later.[16] The use of a high dialysate calcium, 1.75 mmol/L, induced cardiovascular mortality. Ok studied 425 patients with low PTH values who were dialyzing against a high dialysate calcium, which is greater than 1.5 mmol/L. He then randomized them to 1.25 mmol/L or 1.75 calcium baths. Those dialyzed against 1.75 had faster progression of coronary artery calcification compared to those dialyzed against the 1.25 mmol/L bath.[17] We just published an editorial about that paper in *Nature Reviews Nephrology*.[18] We talk about the risk of a high dialysate calcium and, at the end of the piece, we talk about perhaps developing an inline arterial blood ionized calcium sensor to feed back and adjust the individual's dialysate calcium concentration with the goal of achieving an optimal calcium bath for that patient. I think this is where we have to go, not only with calcium but potassium. We have to avoid these large gradients inducing what Dr. Collins has termed "the perfect storm" for arrhythmogenesis.

DR. BLOCK: Yes, I agree. Pieter, I want to hear your thoughts on that issue, particularly as it relates to calcimimetic-induced low serum calcium. As you know, it's really common for people on a calcimimetic to have a low normal, if not overtly low, serum calcium. The temptation, I think, under these conditions is to increase the dialysate calcium. What do you think about that approach and about what we need to learn?

DR. EVENEPOEL: It is certainly an important point. We increasingly use calcimimetics to control the PTH levels. Of course, one of the side effects is the lowering of the calcium. Of course, heating the discussion, calcium and especially the calcium gradient over the membrane is really determining the calcium flux during dialysis, so you can envision that a patient with hypocalcemia following calcimimetic treatment will face an increased calcium influx during dialysis. This increased calcium influx can be hypothesized to offset any advantage of calcimimetic treatment. I certainly would advocate that, at this time, we shouldn't be that afraid of low calcium levels in people treated with cinacalcet. I think it's not the same. The cardiovascular implications of calcimimetic-induced hypocalcemia may differ from hypocalcemia in calcimimetic-naïve patients, e.g. caused by low calcium intake. Indeed, calcimimetics render the calcium-sensing receptor more sensitive to calcium, as it is reflected by the leftward shift of the calcium set point. We shouldn't be that afraid of hypocalcemia in the setting of calcimimetic treatment, and therefore warrant against correcting this hypocalcemia aggressively, for example, by increasing the calcium dialysate to 1.75 mmol/L.

DR. BLOCK: Thank you, Pieter. Allan, in closing, tell us your thoughts on that particular topic, the facts that both low dialysate calcium can be arrhythmogenic and potentially high dialysate calcium can exacerbate the issues David talked about with too much extracellular fluid calcium and deposition into non-skeletal tissue.

DR. COLLINS: I think the other two have already articulated this. I'm in complete agreement with them. The other issue is with trying to infuse calcium with the dialysate when you've got hypocalcemia induced by, let's say cinacalcet treatment. The challenges, as you load the patient during the dialysis run with ionized calcium, it's going to be a pretty potent PTH calcium sensor stimulator to suppress the PTH even further. We're all trying to sort of balance out how to get them through these low calcium periods without disrupting and causing too many other collateral issues that are going on. Geoff and I have talked many times about trying to treat through hypocalcemia induced by cinacalcet and all the challenges you have to go through. It actually is almost impossible to correct the calcium until the gland and the adaptation of what's happening in the bones has sort of passed. Then, everything sort of stabilizes out. I don't know what everybody else's experience is, but when I tried to do this, it was impossible.

COMPOUNDS DISCUSSED:

dialysate calcium concentrations, calcium-containing phosphate binders, calcimimetics, cinacalcet

DR. EVENEPOEL: I think we should be more patient. I mean, if you lower the calcium with cinacalcet, like you said, you should wait until the bone recovers and is able to normalize calcium levels physiologically again. This takes some time.

DR. BUSHINSKY: We also have to recognize that cinacalcet is altering the set point for calcium PTH release, and we've now changed the thermostat in the room. We've changed it from

Clinical Implications

- **Most dialysis patients are likely to be in positive calcium balance when receiving active vitamin D therapy, especially when receiving calcium-containing phosphate binders.**
- **Once the bone calcium needs for dialysis patients are met, calcium can accumulate in the extracellular fluid and can be deposited in soft tissues including the vasculature.**
- **A low calcium dialysate will cause an efflux of calcium from the patient to the dialysate. This will reduce the patient's calcium levels but it can also have adverse consequences due to a potential increase in parathyroid hormone (PTH) and potentially increasing phosphate.**
- **Dialyzing patients on a low calcium bath to remove excess calcium often reduces their arterial blood ionized calcium and increases PTH. The low calcium levels can also induce cardiac arrhythmia and instability.**
- **The use of a high dialysate calcium concentration can induce cardiovascular mortality.**

70 degrees to 65 degrees, for example. That's what the alteration of the set point is doing, and to try to overcome that change in set point by loading the patient with calcium can't work because what determines the blood level of ionized calcium isn't the calcium content in the body, it's the level of the hormones regulating the calcium concentration. For example, a woman or a patient with primary hyperparathyroidism has a high serum calcium but a total reduction in bone calcium, and is more fracture-prone because the regulatory hormone, which is PTH, is not being properly regulated by calcium.

DR. BLOCK: Yes. I think it's a fantastic point, and one that's great to end with, David, because I think that point really is the critical issue with regard to trying to understand how dialysate calcium manipulation will result in these collateral effects that are unrelated, actually, to calcium balance and the potential harmful effects of trying to achieve this balance concept by manipulating the concentration of dialysate, and thereby neglecting the essential important piece, which is regulation of ionized calcium in the blood, and the consequences of that.

I think it's been a fantastic discussion, honestly. I can't imagine three better people to discuss this topic than the three of you, and I can't thank you enough. It's a fascinating thing, and I hope I'm not misstating when I say that all of us agree that we should have some serious reservations about using low dialysate calcium concentration as a method to achieve neutral calcium balance. Similarly, we have reservations about the use of high dialysate calcium concentration, and I think, at the end of the day, the KDIGO recommendations,[19] an update of which will be available for public comment hopefully within this calendar year, suggest that a 1.25 calcium dialysate is, in fact, a very reasonable approach to balance this issue of kinetics and calcium balance. Thank you all very much.

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