ing force of CMBs during HD (Figure 1). This suggests that patients dialysed against a dialysate total calcium concentration of 1.25 mmol/L, corresponding to an ionized calcium concentration of 1.25 × 0.866 (i.e. 86.6% of 1.25) = 1.08, should have a predialysis plasma-ionized calcium concentration of 1.08 mmol/L and no weight loss in order to achieve a neutral CMB during HD. If the predialysis plasma-ionized calcium concentration is >1.08 mmol/L and there is the need of losing weight (each litre of UF contains about 50 mg of calcium), CMB will be largely negative. In fact, negative CMBs of 200–520 mg have been documented in patients with predialysis plasma-ionized calcium concentrations in the normal range and average UF volumes of 2–3 L during single HD sessions with a dialysate total calcium concentration of 1.25 mmol/L [4–6].

In conclusion, as always, the truth lies in between the two opposite theses [1,2]: on the one hand, it is true that over the past 25 years, since the advent of calcitriol, virtually all HD patients have absorbed a significant portion of dietary and phosphate binder calcium ingested between dialyses and thus are able to achieve a positive CMB between dialyses [2]; on the other hand, it is also true that lowering the dialysate calcium concentration too much could expose them to very negative CMBs due to the diffusion gradient that in this case would be from plasma to the dialysate. Thus, there is probably no one optimal dialysate calcium concentration [1]. Ideally, the dialysate calcium concentration would be adapted to each patient’s needs [1]. This being neither feasible in most dialysis settings, nor cost-effective [1], the time has probably come to ask the technology to design a ‘calcium profiling’ model, similar to what has been done for sodium and UF: the dialysate total calcium concentration should be, for instance, 1.25 mmol/L at the start of dialysis and 1.5 mmol/L at the end of dialysis, with a time-profiled increase of calcium concentrations between the two limits. An adequate ‘calcium profiling’ would be the right compromise between the need to guarantee cardiovascular stability during HD, the goal to maintain normal bone turnover and mineralization and the goal to avoid the risk of calcium overload and vascular calcification.

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Relevance of QT dispersion in haemodialysis patients

Sir,

I read with great interest the recent papers by Drueke and Touam [1] and Gotch [2] in the pro/con debate section of
the journal on calcium balance in haemodialysis. The considerations of the two papers are excellent and appropriate about the necessity to verify the calcium balance in dialysis for potential harmful effects of low calcium dialysate. Particularly, Druke and Touam describe this as ‘low calcium concentration may be associated with cardiac rhythm disturbance’ [1] and Gotch suggests this as ‘the correct QT interval (QT-c) in the EKG has been reported to increase with C₄₅Ca²⁺ < 3’. Several papers show that dialysis per se produces QT-c increases for concomitant relative hypokalaemia and negative balance of calcium after dialysis [3–7]. Gussak and Gussak [8] postulated that patients undergoing haemodialysis might experience a progressive diminution and inhibition of the potassium channels that might lead to a reduction of the ‘cardiac repolarization reserve’.

Another relevant issue is the QT dispersion (QT-d), which is defined as the difference in duration between the longest and shortest QT interval for a given set of electrocardiogram leads. This was originally proposed as a direct measure of the regional heterogeneity of myocardial repolarization. It was thought that increased repolarization heterogeneity or QT-d predisposed to re-entrance pathways and ventricular arrhythmias. More recent studies disprove this theory, however, and suggest that QT-d instead reflects differences in heart dipole projections and abnormalities of T-wave loop morphology. It has been proposed that QT-d be viewed more as an approximation for repolarization abnormalities rather than a true measure for regional heterogeneity of myocardial refractoriness [9]. Beaubien et al., in a retrospective study, determined the prognostic value of QT-d in predicting total, cardiovascular and arrhythmia-related mortality in ESRD patients initiating dialysis [9]. A total of 147 patients were studied for a period of 5 to 9 years. In Cox modelling, QT-d was an independent predictor of total (relative risk [RR] = 1.53; difference for RR = 50 ms; P = 0.0001) and cardiovascular mortality (RR = 1.57; difference for RR = 50 ms; P = 0.028) and was a trend toward arrhythmia-related mortality (P = 0.061).

Bleyer et al. [10] calculated that 47.9% of 276 deaths (6.3% of total deaths) was due to sudden death in dialysis patients in the CMAS study, and 45.1% of patients with sudden death showed QT-d ranged 40–90 and over 90 ms, respectively. Karnik et al. [11] documented 400 cardiac arrests among the 5 744 708 haemodialysis treatments provided during the 9-month study period. This corresponds with an incidence rate of 0.007% (or 7 per 100 000) [11]. In Italian dialysis patients, the same incidence rate represents a range of 50 to 100 deaths per year.

On the other hand, my colleague and I showed that, at study entry, 28 out of 132 (21%) patients had evidence of cardiac calcification (CAC), while true progression of CAC was detected in 81 (61%) patients by the end of the 12-month follow-up. Of interest, at univariate analyses, CAC progression was also associated with a significantly greater increase in QT-d. Indeed, every 20 units increase in CAC corresponded to a significant 23% (95% CI = 1.12–1.27; P < 0.001) increase in the risk of experiencing 1 ms in QT-d, respectively (unpublished data).

Finally, Curtis et al. [12] from Duke University explored a large prescription claims database that included 4.8 million patients; they discovered unacceptably high rates of prescription of QT-prolonging medications and concomitant therapy with two or more QT-prolonging drugs. The analysis included 50 medications associated with QT interval prolongation and 26 agents, which inhibited hepatic or renal clearance of these medications.

The information obtained in the papers by Druke and Touam [1] and Gotch [2] is, for this issue, very important, considering that, more than a few years ago, we were educated to use at first a high dialysate calcium, then a very low concentration allowing the intravenous use of vitamin D; and finally, we learned to understand that we needed to be less dogmatic. All this occurred without paying due attention to sudden death by cardiac arrhythmias for acquired long QT syndrome [8].

For this and for the high possibility of prescription of drugs that lengthen the QT interval, we need to put greater emphasis on the recommendation of a better control of the conditions favouring the arrhythmias QT, acquired long QT syndrome and sudden death.

Acquired long QT syndrome is one of the many mechanisms of sudden death in nephrology. The arrhythmogenic potential of acquired long QT syndrome in renal patients, because of electrophysiological remodelling of the heart due to concomitant cardiovascular disease, and the excessive potential exposure to the multiple (often excessive and pro-arrhythmogenic) medications and/or their abnormal excretion or metabolism, are today still neglected conditions that we need to underline.

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Reply

Dear Sir,

I want to thank Dr. Basile for his interesting comments and data concerning selection of optimal dialysate inlet calcium concentration (CdiCa++). Firstly, I would like to make the point that both he and Dr. Drueke have misinterpreted my message when they state that I have recommended ‘indiscriminate’ lowering of dialysate calcium (CdiCa++). The frequency distribution I reported [1] for optimal modeled CdiCa++ ranged from 1.5 to 3.5 mEq/L. It was based on ‘discriminate’ assessments of: the levels of: (i) Ca++ absorption as a function of Ca++ intake and doses of Vit D3 analogues; (ii) Ca++ removal as a function of the true Ca++ diffusion gradient at the dialyzer inlet [corrected for a Donnan coefficient and decrease in inlet plasma Ca++ (ΔCpiCa++)]; (iii) Ca dialysance; (iv) ultrafiltration rate and (v) treatment time.

Dr. Basile claims to have revealed ‘the truth’ with respect to optimal CdiCa++, strongly emphasizing that his data show the driving force is the diffusion gradient. He provides some ‘back of the envelope’ example calculations resulting in negative intradialytic CaMB depending on CpiCa++ and advises a calcium-profiling algorithm with CdiCa++ increasing from 2.5 to 3.0 during dialysis.

In support of these conclusions, he showed a data set obtained in 11 patients dialysed against CdiCa+++ = 3.0 mEq/L. The gradient is plotted as a dependent variable of total flux and defined as CdiCa++ minus the predialysis plasma Ca++ (CpiCa++) in accordance with (CdiCa++ − CpiCa++). This is not a rigorous definition of the diffusion gradient since the driving force is (CdiCa++ − M(CpiCa++)) where M is the mean CpiCa++ which in turn is a complex function of the amount of flux and miscible buffer pool coefficient [1]. Invalidity of the diffusion gradient he reports is further demonstrated by the fact that the total flux for 4- and 8-hour dialyses was equal with the same gradient, which is mathematically impossible.

The data reported by Dr. Basile were replotted with gradient, the independent variable, on the x axis and flux on the y axis as shown in Figure 2 where the 4- and 8-hour values are plotted as a single species. The actual data points for the regression we reported [1] also show R2 = 0.9106. The purpose of this plot is to directly visualize the validity of the diffusion gradient. When the diffusion gradient = 0, flux is purely convective so flux at this point must be negative and equal to the product of total Qf × (KMP − CpiCa++). Note that, in the data, we reported flux = −110 mg when gradient = 0 corresponding to about 2.5 L of ultrafiltrate. In contrast, the Basile regression shows Ca++ flux = +250 mg when the calculated diffusion gradient = 0 which indicates one or more systematic errors in calculation of flux and/or gradient. If the observed Basile regression were used to achieve an intradialytic CaMB = −100 mg (which is a minimal estimate of the average modeled magnitude required), the diffusion gradient must be −0.80 mEq/L so with average CpiCa++ 2.25 mEq/L, the required CdiCa++ would be 1.45 mEq/L, far lower than the median value we modeled of 2.25 mEq/L.

![Figure 2](https://academic.oup.com/ndt/article/25/4/1357/1861143/fig2)

**Fig. 2.** Basile data (1) re-plotted with driving force on x-axis and reported total flux on y-axis; it is compared to data we obtained for the plot reported in our manuscript (2); if the driving force is calculated correctly, the total flux must be negative and equal to the convective flux when gradient = 0 as in the curve (2) where the value −110 represents approximately 2.5 L of ultrafiltrate; there must be one or more systematic errors in the Basile data since total flux is +250 mg when gradient = 0.