Comparison between two dialysate calcium concentrations on parathormone level in hemodialysis patients with and without valvular calcification

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Abstract: Cardiovascular stability, renal bone disease, vascular and valvular calcification are main issues regarding the role of calcium in hemodialysis (HD) patients so the choice of dialysate calcium concentration is able to influence many of the most important factors in the successful management of chronic HD patients. Accordingly, the present study was designed to investigate the relative role of different dialysate calcium concentrations on parathyroid hormone levels and cardiovascular stability in HD patients. This study was conducted on two groups, 40 patients each. Group (A) including patients dialyzed with low calcium dialysate (1.25mm/l) for 3 months and Group (B) including patients dialyzed with high calcium dialysate (1.75 mm/l) for 3 months. Mean serum calcium of group A was significantly lower than that of group B ($p< 0.05$) while parathyroid hormone (PTH) of group A was slightly higher than that of group B but still insignificant ($p = 0.07$), also mean calcium supplement dose required daily by group A was significantly higher than that needed by group B ($p < 0.05$). Both mitral and aortic valves calcification were present more in group B than group A (17.5% versus 7.5%) ($p= 0.176$) but still insignificant. In high dialysate calcium concentration group, PTH was significantly increased in patients with valvular calcification when compared to those without ($p = 0.001$). Duration of HD, PTH, phosphorus level and the calcium phosphorus product had a positive correlation with the valvular calcification. There were no significant correlations between level of serum calcium, ionized calcium and valvular calcification. In conclusion, dialysate calcium concentration is one of the factors that are used to control PTH level in HD patients together with phosphorus binders and vitamin D metabolites. High PTH, together with high phosphorus level, is deleterious as it helps in formation of valvular calcification.

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1. Introduction

Cardiac diseases are the major cause of death in HD patients (La France *et al.,* 2006). Persons with CKD are predisposed to three types of cardiovascular disease (CVD) namely atherosclerosis, arteriosclerosis and cardiomyopathy. Chronic uremic cardiomyopathy may manifest as concentric left ventricular hypertrophy or dilatation, and may result in diastolic or systolic dysfunction. These disorders are associated with the subsequent development of cardiac failure and death (Parfrey and Foley, 2005).

HD patients have a rate of arrhythmias 40 times greater than the general population (Al-Khatib *et al.,* 2007). Arrhythmia is decreased by prolonged sessions with low ultrafiltration rates, careful dry weight titration and administration of oxygen and β blockers (Fukuta *et al.,* 2003).

Digitalis therapy with acetate containing dialysate and a high calcium phosphate product may be correlated with increased incidence of ventricular arrhythmias (Antonio *et al.,* 2008).

The presence and extent of vascular calcification are predictors of CVD and all cause mortality in stable end-stage renal disease patients on HD (Rennenberg *et al.,* 2009). Calcium based phosphate binders and high doses of vitamin D, may contribute to development of vascular calcifications (Goodman, 2004). Calcification in the vessel walls occur in 2 sites, the intima mainly associated with occlusion of the vessels and the media which is associated with vascular stiffness. Both are responsible for increase mortality in patients with CKD (Ketteler *et al.,* 2005).

Hyperphosphatemia is a strong risk factor for CVD mortality in HD patients. High extracellular phosphate may initiate osteogenic transformation and calcification through production of calcium-phosphate crystals especially if associated with calcitriol elevation (Stubbs *et al.,* 2007).

The dialysate calcium concentration should be viewed as part of the integrated therapeutic regimen to control renal osteodystrophy and maintain normal mineral metabolism. The role of calcium dialysate lies in 2 main issues; CVD stability and renal bone disease and vascular calcification (Christopher, 2008). KDOKI bone guidelines recommended a target predialysis corrected serum calcium within the normal range of 9.5 mg% and dialysate calcium concentration of 1.25 mmol/l. European best practice recommended the

dialysate calcium concentration of 1.5 mmol in patients with frequent episodes of intradialytic hypotension (Table 1) (European Best Practice Guidelines, 2007). There is however a considerable variations in recommendations on a global basis.

Table 1: Advantage and disadvantage of different dialysate calcium concentration.

	Lower Dialysate calcium (1.25 mmol/L)	**Higher Dialysate calcium (1.75 mmol/L)**
Advantages	Reduces risk of hypercalcemia Allows greater use of vitamin D and calcium-containing phosphate binders Benefit in adynamic bone disease	Improves hemodynamic stability. Suppression of PTH. Beneficial for bone protection in nocturnal HD.
Disadvantages	Potential for negative calcium balance and stimulation of PTH Increase in intra-dialytic hypotension	Greater risk of hypercalcemia Limits use of vitamin D and calcium based binders Possible risk of vascular calcification

The aim of this study was to investigate the relative role of different dialysate calcium concentrations on PTH level in HD patients with and without valvular calcification.

2. Patients and Methods

This study was conducted on 80 HD patients. They were divided into 2 groups according to dialysate Ca concentration used in HD. Group A (n= 40) used 1.25 mmol/L and group B (n= 40) used 1.75 mmol/L for 3 months. The dialysate composition in both groups was otherwise the same.

All patients will be subjected to full history taking, clinical examination, hematological and biochemical investigations and measurement of PTH level (Endras *et al.,* 1989), calcium-phosphorus product (CaxP) and phosphorus (Farrel, 1987). Cardiovascular assessment including ECG and transthoracic echocardiography were also investigated.

Statistical analysis

Results are expressed as mean ± standard deviation, or number (%). Comparison of mean values of different variables in the two groups was performed using unpaired t test. Comparison between categorical data was performed using Chi square test. Correlation between different parameters was performed using Pearson correlation coefficient. p value ≤ 0.05 was considered significant. SPSS (version 16) was used in data analysis.

3.Results

The demographic and clinical features of the two studied groups were statistically comparable ($p > 0.05$) except in the mean calcium dose where it was significantly higher in group A than in group B ($p = 0.024$) (Table 2). Also most of laboratory investigation tests and all echocardiographic findings were statistically comparable except in plasma hemoglobin, serum total calcium and ionized calcium where there was a statistical significant difference between both groups ($p = 0.039$; 0.011 & 0.031, respectively) (Tables 3-4).

In both groups, patients with valvular calcification showed higher levels of HDx duration, serum PO_4 and $CaxPO_4$ than patients without valvular calcification [group A; p= 0.001; 0.042 & 0.021, respectively and in group B; p = 0.001; 0.041 & 0.02, respectively), in addition to PTH in group B ($p = 0.001$) (Table 5). The prevalence of valvular calcification was significantly higher in group B [27 (67.5%)] than in group A [16 (40%)] ($p = 0.001$) (Table 6).

A positive correlation was observed between duration of HD and valvular calcification in both groups. However it is stronger in group A than B (r= 0.8 vs 0.6 with $p < 0.05$). Also positive correlation was observed between serum PO_4 and valvular calcification in groups A and B (r= 0.69 & r= 0.72; $p < 0.05$, respectively). $CaxPO_4$ showed also positive correlation with valvular calcification in groups A and B (r= 0.54; r= 0.65; $p < 0.05$, respectively).

Table 2: Demographic features and clinical data of the two studied groups.

	Group A (n= 40)	**Group B (n= 40)**	***p* value**
Age (yrs.)	53.95 ± 10.08	46.55 ± 10.58	0.201
Gender (F/M)	13/27 (32.5/67.5%)	16/24 (40/60%)	0.379
HDx Duration (yrs)	5.56 ± 3.51	4.83 ± 2.58	0.291
SBP (mmHg)	124.25 ± 18.10	129.38 ± 18.12	0.194
DBP (mmHg)	75.75 ± 10.89	73.50 ± 12.05	0.383
Pulse (min.)	86.80 ± 7.22	86.53 ± 7.15	0.865
Intradialytic HTN	9 (22.5%)	6 (15.0%)	0.394
Ca dose (gm/day)	2.97 ± 1.03	2.45 ± 0.95	0.024*
Alphacalcidol dose (µg/wk)	2.52 ± 0.71	2.65 ± 0.65	0.451

Data are expressed as mean ± SD or number (%). *p< 0.05= significant.

Table 3: Comparison between mean values of different laboratory data in the two studied groups.

	Group A (n= 40)	Group B (n= 40)	*P* value
Urea (mg%)	123.20 ± 42.64	118.23 ± 40.41	0.594
Creatinine (mg%)	9.80 ± 5.88	8.43 ± 2.21	0.171
Hb (g%)	8.64 ± 1.49	9.31 ± 1.38	0.039*
Albumin (g%)	3.48 ± 0.43	3.40 ± 0.41	0.425
Total Ca (mg%)	7.93 ± 1.01	8.52 ± 1.01	0.011*
PO_4 (mg%)	5.15 ± 1.69	5.14 ± 1.21	0.976
Ionized Ca (mg%)	1.09 ± 0.10	1.14 ± 0.11	0.031*
Ca×PO_4	41.05 ± 14.70	43.79 ± 11.91	0.363
ALP (U/L)	182.45 ± 98.03	178.68 ± 145.31	0.892
PTH (mg%)	492.75 ± 282.57	389.33 ± 223.24	0.073

Data are expressed as mean ± SD. *p< 0.05= significant.

Table 4: Comparison between mean values of different echocardiographic data in the two studied groups.

	Group A (n= 40)	Group B (n= 40)	*P* value
AO (mm)	29.63 ± 4.40	30.10 ± 4.66	0.640
LA (mm)	39.68 ± 6.56	40.05 ± 5.61	0.784
EDD (mm)	51.10 ± 6.66	50.04 ± 10.08	0.580
ESD (mm)	37.25 ± 8.83	38.09 ± 9.24	0.623
FS (%)	37.15 ± 9.07	34.75 ± 5.54	0.157
EF (%)	56.73 ± 8.91	57.40 ± 8.30	0.727
IVSTd (mm)	11.45 ± 2.34	11.58 ± 1.85	0.792
PWTd (mm)	11.53 ± 1.92	11.51 ± 1.56	0.975

Data are expressed as mean ± SD.

Table 5: Comparison between mean values of serum calcium, phosphorus and PTH in the two studied groups with and without valvular calcification.

	Group A (n= 40)			Group B (n= 40)		
	With	**Without**	***P* value**	**With**	**Without**	***P* value**
HDx Duration	8.50 ± 2.50	3.15 ± 2.08	0.001**	6.17 ± 2.29	3.00 ± 1.70	0.001**
Total Ca	8.24 ± 1.15	7.68 ± 0.82	0.082	8.76 ± 0.87	8.19 ± 1.12	0.082
PO_4	5.69 ± 1.08	4.71 ± 1.14	0.042*	5.56 ± 1.14	4.76 ± 1.04	0.041*
Ionized Ca	1.12 ± 0.10	1.07 ± 0.09	0.098	1.15 ± 0.11	1.12 ± 0.11	0.395
Ca×PO_4	46.89 ± 15.25	36.17 ± 12.85	0.021*	48.70 ± 12.20	38.98 ± 11.42	0.020*
PTH	517.50 ± 251.43	472.50 ± 310.1	0.623	491.35 ± 235.57	251.29 ± 99.84	0.001**

Data are expressed as mean ± SD. *p< 0.05= significant. **p< 0.01= highly significant.

Table 6: Prevalence of valvular calcification in the two studied groups.

	Group A (n= 40)	Group B (n= 40)	*P* value
Aortic	6 (15.0%(	10 (25.0%)	0.065
Mitral	7 (17.5%)	10 (25.0%)	0.098
Both	3 (7.5%)	7 (17.5%(	0.176
None	24 (60 %)	13 (32.5%)	0.014*

Data are expressed as number (%). *p< 0.05= significant.

4.Discussion

The choice of dialysate calcium concentration is able to influence many of the most important factors in the successful management of chronic HD patients (Christopher, 2008). Long-term use of dialysate calcium with 1.25 mmol/L would be associated with relatively lower serum calcium concentrations, which would lead to more rapid elevation of iPTH, progression of secondary hyperparathyroidism (Hwang *et al.,* 2008) and also might be associated with more frequent episodes of hypotension and cardiac rhythm disturbances. Probably, the most life-

threatening episodes are ventricular arrhythmias in association with concomitant hypokalaemia (Severi *et al.,* 2008).

The use of high dialysate calcium concentration, 1.75 mmol/l, is associated with a positive calcium balance. When associated with concomitant use of calcium-containing phosphate binders, it has a serious effect on vascular calcification, arterial stiffness and cardiac relaxation (Malberti and Ravani, 2003). Accordingly, the present study designed to investigate the relative role of different dialysate calcium concentrations on PTH level and cardiovascular stability in ESRD patients on regular HD.

This study was conducted on 80 patients dialysed with a dialysate whose Ca concentration was 1.25 mmol/l (group A, n= 40) and 1.75 mmol/l (group B, n= 40) for at least 3 months. Each group was divided according to absence or presence of valvular calcification detected by transthoracic echocardiography.

In our study, patients in both groups with valvular calcification had a longer HD duration, higher serum calcium, ionized calcium, PO_4, $CaxPO_4$ product and higher PTH than those without valvular calcification. A positive correlation was observed between duration of HD and valvular calcification in both groups. However it is stronger in group A than B (r= 0.8 vs 0.6 with $p< 0.05$) i.e. longer HD duration is needed by low dialysate calcium to develop valvular calcification. Also, the mean calcium supplement dose of group A was significantly higher than that of group B, in order to maintain the level of serum calcium within the KDIGO guidelines. Also positive correlation was observed between serum PO_4 and valvular calcification in both groups, but stronger in B than A (r= 0.72 vs 0.69; $p< 0.05$). $CaxPO_4$ showed also positive correlation with valvular calcification in both groups however, stronger in group B than A (r= 0.65 vs 0.54, $p < 0.05$) meaning that even minor increase in level of PO_4 will be associated with increased incidence of valvular calcification even in the low dialysate calcium group.

The higher phosphorus level, calcium phosphorus product and prevalence of valvular calcification within both groups however higher PTH level is associated with a higher prevalence valvular calcification in group B only. These results are in agreement with those of Shaarawy *et al.* (2012) who found that valvular calcifications were present in older patients, with longer HD duration, higher P and $CaxPO_4$ and lower EF%. However there were no association between serum calcium and PTH and valvular calcifications contrasting with our results.

Fernandez *et al.* (1995) reported that lowering of dialysate calcium from 1.75 to 1.25 mmol/L for six months HD and after the dialysate change led to worsening of secondary hyperparathyroidism.

Haris and Robert (2003) found that increasing the dialysate calcium from 1.5 to 1.75 mM led PTH level to fall significantly from 39.6 to 16.6 PM, whereas serum calcium increased from 2.27 to 2.41 mM. There was no significant change in serum PO_4. So, they concluded that increasing dialysate calcium can safely treat hyperparathyroidism with minimal risk of complications.

Lezaic *et al.* (2007) lowered dialysate calcium in order to stimulate bone turnover in HD with biochemical signs of adynamic bone disease (hypercalcemia, normal alkaline phosphorus and intact PTH (<140 pg/ml) and to decrease hypercalcemia in patients with secondary hyperparathyroidism (hypercalcemia, high alkaline phosphatase and PTH > 400 pg/ml), thus permitting the use of calcium containing PO_4 binders and vitamin D metabolites.

Molina *et al.* (2008) found that increasing dialysate calcium led to better control of secondary hyperparathyroidim without affecting calcium and $CaxPO_4$ levels thus enabling the reduction of dosage of vitamin D metabolites.

Ching *et al.* (2010) categorized 717 non-diabetic HD patients into 3 groups based on dialysate calcium concentration; high 3-5 mEq/l standard, 3 mEq/l or low 2.5 mEq/l and high calcium dialysate and found that it was associated with malnutrition, inflammation and earlier mortality.

Rufino *et al.* (2003) illustrated that $CaxPO_4$ product > 43 mg^2/dl^2 was the optimal value in terms of sensitivity and specificity for predicting the presence of valvular calcification in these patients.

Our echocardiographic findings were statistically comparable in the two groups. Their prevalence of valvular calcification showed no statistical significance except in the number of those without valvular calcification which was higher in group A (60% vs 32.5%, p= 0.014).

Valvular calcification is a marker of systemic CVD in CKD stage 5 patients (Raggi *et al.,* 2011) and is found prevalent 4-5 times higher than in the general population (Ribeiro *et al.,* 1998). Most commonly reported risk factors aging, longer HD duration, hypercalcemia, hyperphosphatemia, increased $CaxPO_4$ product, hyperparathyroidism, hypertension, DM, dyslipemia and serum inflammatory markers (Raggi *et al.,* 2002).

Echocardiography is recommended by KDOQI for assessment of cardiac valve morphology and function and calcification in HD patient (Moe *et al.,* 2009). Torun *et al.* (2005) assessed his patients by an echocardiogram for the presence of valvular calcification. They were detected in 46% of patients (6% mitral, 14% Aortic and 20% both valves).

Strózecki *et al.* (2005) found no difference with respect to calcium, PO_4, PTH in patients with and without valvular calcification. However, incidence of $CaxPO_4$ product was higher in patients with valvular calcification. Tarras *et al.* (2006) and Volkov *et al.* (2009) showed the reverse: higher levels of serum calcium, PO_4 and $CaxPO_4$ product as compared with patients without valvular calcification.

In contrast to our study, Shaarawy *et al.* (2012) found that the EF was significantly higher in patients with no valve calcification compared to patients with ($p=0.02$). Also, the ESD was significantly higher in the group with, meaning some degree with ventricular enlargement, and once calcification happens, changes in echo parameters start. Cardiovascular calcification is associated CVS disease and mortality among HD patients and the disorder progresses rapidly once established (Raggi *et al.,* 2011).

In our study, intradialytic hypotension detected by blood pressure 100/60 starting to occur within one hour of start of HD session and reaches, a peak at 120 minutes. Patient may complain of dizziness, headache, vomiting and muscle cramps. It was observed in 9 patients in group A and 6 patients in group B. One predisposing factor to it was low calcium dialysate (Sherman *et al.,* 1986). Irregular rhythm was observed in 5 patients in group A and 1 patient of group B (2.5%) so the low dialysate calcium (12.5%) was associated with higher incidence of irregular rhythm, the same results were found by Nappi *et al.* (2000).

There were limitations to our study; small number of patients, short duration of the study, no fixation of the phosphate burden (calcium acetate or calcium carbonate), no available echocardiogram before initiation of HD, limited assessment of KT/V regularly for all patients. However, we agree with Palmer (2001) recommendations that dialysate calcium concentration should be tailored to the individual patient.

In conclusion, dialyzate calcium concentration is one of the factors that is used to control PTH level in HD patients together with phosphorus binders and vitamin D metabolites. High PTH, with high phosphorus level, is deleterious as it helps in formation of valvular calcification, and should be controlled as much as possible.

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