Conjunctival and Corneal Calcifications in Hemodialysis Patients: Is There Any Correlation With Vascular Calcifications?

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Abstract: Background: Vascular and soft tissue calcifications are prevalent in hemodialysis patients. Mortality of hemodialysis patients are likely linked to both vascular and soft tissue calcifications. The aim of current study is to find relation between vascular calcificationswithconjunctival and corneal calcifications (CCC) and their relations to biochemical parameters in hemodialysis patients. **Methods:** A total of 88 patients on regular hemodialysis were studied for vascular calcifications using lateral abdominal x ray for aortic calcifications and for CCC using slit lamb examination. The cohort was divided according to the presence or absence of vascular calcifications and again according to the presence or absence of CCC. Clinical, biochemical and imaging parameters were compared among studied groups. **Results:** Serum phosphorus, calcium x phosphorus products (Ca x P), intact parathormone (iPTH) and urea post dialysis were significantly different when compared patients with vascular calcifications against those without. Serum phosphorus, (Ca x P), (iPTH), body mass index and duration of dialysis were significantly different when compared patients with CCC against those without. Regression analysis and receiving operation characteristic (ROC) curve demonstrated that (iPTH) was the only predictor for both vascular and CCC with cut off values 702 Pg/ml and 533 Pg/ml andarea under the curve (AUC) of 0.706 and 0.786 respectively. **Conclusions:** Intact PTH is the predictor of both vascular and CCC. Soft tissue calcifications may precede vascular calcifications in hemodialysis patients. Intact PTH levels should not exceed 533 Pg/ml in hemodialysis patients. Meta-analysis study is needed to confirm our results and assess other sites for soft tissue calcifications and also to assess the effect of controlling (iPTH) on regression of both vascular and CCC.

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Key words: Hemodialysis, Vascular calcifications, Conjunctival and corneal calcifications (CCC), Soft tissue calcification.

1. Introduction:

Chronic kidney disease (CKD) is almost constantly associated with a systemic disorder of mineral and bone metabolism, which has recently been named chronic kidney disease – mineral and bone disorder (CKD-MBD). It is manifested by either one or a combination of biochemical abnormalities (abnormal calcium, phosphorus, iPTH, or vitamin D metabolism), bone abnormalities (abnormal bone turnover, mineralization, volume, linear growth, or strength) and vascular or other soft tissue calcification. (1). Vascular calcification is common in patients with advanced chronic kidney disease and is associated with poorer outcomes. Although the pathophysiology is not completely understood, it is clear that it is a multifactorial process involving altered mineral metabolism, as well as changes in systemic and local factors that can promote or inhibit vascular calcification, and all of these are potential therapeutic targets (2). The lateral abdominal radiography can be used to detect the presence or absence of vascular calcification, as reasonable alternative to computed tomography based imaging in patients with CKD stages 3–5. Lateral abdominal radiography is aneasier technique with a reasonable sensitivity, as compared with the more expensive CT-based techniques and may yield comparable information (3). Soft tissue calcification is a prominent feature in CKD patients (4). CCC is well recognized as a metastatic calcification in patients undergoing hemodialysis (5). Evaluation of CCC score is an easy, fast, and noninvasive method. It seems that CCC score can be used as an additional tool to assess the status of extra skeletal calcification in dialysis patients (6). Vascularcalcification is strongly associated with CCC. The severity of CCC is an independent predictor for all-cause 1-year mortality in maintenance hemodialysis patients. A simple test to evaluate CCC may be an inexpensive and non-invasive method that allows the identification of patients with higher mortality risk. This information can be used to guide the management of maintenance hemodialysis patients (7). The aim of our work is to study the possible

relationship between CCC with vascular calcification and their relations to biochemical parameters in chronic hemodialysis patients.

2. Patients and methods:

This study was carried out on eighty-eight patients in Ahmed Maher teaching hospital. Patients with at least one year duration on regular dialysis were included. The study followed the ethical standard of the institute and it was approved by the ethical committee, as well as informed consent was obtained from all patients. The following patients were excluded from the study, Patients with malignancy, primary hyperparathyroidism, granulomatous disorders like tuberculosis or sarcoidosis and any condition that may affect calcium and phosphorus homeostasis. All subjects underwent full history taking and clinical examination. Including weight, height and measuring blood pressure. Mean arterial pressure (MAP) before and after dialysis. It was calculated as {(2 x diastolic blood pressure (mmHg) + systolic blood pressure (mmHg)}/3. BMI Was calculated as weight (Kg)/ {Height (m)}^{2}. Also they underwent laboratory investigations including serum calcium, phosphorus and intact parathormone (iPTH). For detection of vascular calcification abdominal x-rays (lateral view on lumbo-sacral spine) to detect calcification of abdominal aorta was done for all patients. Slit lamp examination was done to all patients to detect CCC (Figure 1). The same observer, who was blinded to clinical data, evaluated ocular calcifications in all subjects. There were no clinically apparent eye diseases that can cause ocular calcifications in the study subjects. All patients under hemodialysis more than one year using standard solution contained 1.75 mmol/L of calcium. Hemodialysis was performed using synthetic or semisynthetic membranes, and bicarbonate dialysate. Weekly hemodialysis treatment duration was tailored individually between 10 and 15 hours. Calcium, phosphorus binders and active vitamin D were administered to all patients according to calcium, phosphorus, and iPTH values. Target values were as follows: calcium, 8.4 to 9.5 mg/dl (2.10 to 2.37 mmol/L); phosphorus, 3.5 to 5.5 mg/dl(1.13 to 1.78 mmol/L); Ca × P less than 55 and iPTH 2 -9 times normal values. Patients were divided according vascular calcification into two groups, those with vascular calcification and those without. Comparison of clinical and laboratory data was done between the two groups. The same cohort was divided again according CCC into two groups, those with CCC and those without and the same comparison was done between the two groups.

Statistical evaluations:

We used the statistical package of social signs (SPSS, version 16) to perform the analysis. Categorical data were presented as number and percentages and continuous variables as means ± standard deviation (SD). Chi-Square test was used for categorical variables. Student t test or Mann-Whitney test was used as appropriate for comparison between two quantitative variables. Regression analysis was performed to detect the possible predictors of vascular and CCC. Receiving operation characteristic (ROC) curve was constructed to detect cut off value and area under the curve (AUC) for best predictors of vascular and CCC with sensitivity, specificity, positive predictor value (PPV) and negative predictor value (NPV). P value ≤ 0.05 was considered significant.

3. Results:

This study included 88 patients with end stage renal disease on regular hemodialysis more than one year. Epidemiological data and base line characteristics were shown in table 1. The cohort was divided according tovascular calcification into two groups, those without vascular calcifications 59 patients (67 %) and other group with vascular calcification 29 patients (33 %) (Figure2). Table 2 showed comparison between the studied groups as regards vascular calcifications. Serum phosphorus, Ca x P, iPTH and urea post dialysis were the only parameters showed significance difference among the studied groups. Logistic regression analysis was done among the significant parameters to detect the predictor of vascular calcification and it showed that iPTH is the predictor of vascular calcification with P value of 0.014. ROC curve was constructed to detect the cut off value of iPTH to detect vascular calcification (Figure 3). It showed best cut off value702 pg/mlwith AUC of 0.706 (95 % CI: 0.595 – 0.817) and P value of 0.002. It showed 79 % sensitivity, 60 % specificity, 49 % PPV and 85 % NPV. The cohort was divided again according CCC into two groups those without CCC 36 patients (41 %) and those with CCC52 patients (59 %) (Figure2). Table 3 showed comparison between the studied groups as regards CCC. Serum phosphorus, Ca x P, iPTH, BMI and duration of dialysis were the only parameters showed significance difference among the studied groups. Logistic regression analysis was done among the significant parameters to detect the predictor of CCC. iPTH was found to be the best predictor of CCC with P value 0.006. ROC curve was constructed to detect the cut off value of iPTH to detect CCC (Figure 4). It showed cut off value of 533 pg/ml with AUC 0.786 (95 % CI: 0.689 – 0.883) and P value 0.0001. It showed 80 % sensitivity, 67 %

specificity, 78 % PPV and 71% NPV. Among the 29 patients with vascular calcifications there were 21 (72 %) patients showed CCC; however among the 52 patients with CCC there was 21 (40 %) patients showed vascular calcifications. It means that CCC is highly associated with vascular calcifications; however the reverse did not show this association.

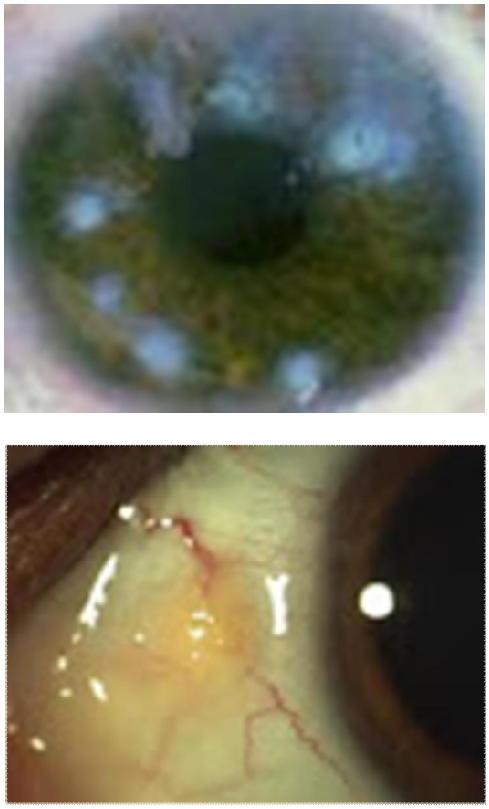

Figure 1: Slit lamp examination showed conjunctival and corneal calcifications

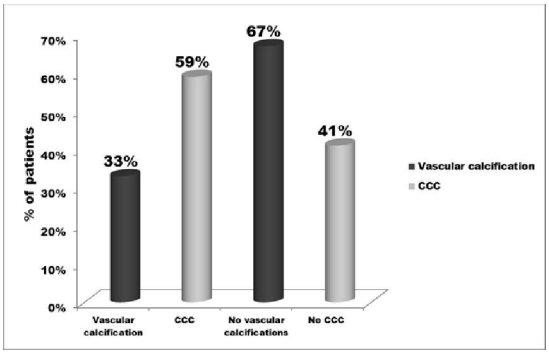

Figure 2: Distribution of vascular and conjunctival and corneal calcifications among patients

%; Percentage, CCC: Conjunctival and corneal calcification

Table 1: Base line characteristics of all patients.

Variables	Minimum	Maximum	Mean	±SD
Age (Years)	17.00	74.00	49.55	12.48
Gender Male No (%) Female No (%)	-	-	47(53.4%) 41(46.6%)	-
BMI	15.97	34.37	27.30	3.76
Duration of dialysis (Years)	2.00	17.00	5.61	3.02
MBP Predialysis (mmHg)	73.33	136.67	104.77	15.07
MBP Post dialysis (mmHg)	63.33	126.67	87.39	13.22
Urea pre dialysis (mg/dl)	70.00	248.00	1.52	38.93
Urea post dialysis (mg/dl)	30.00	110.00	70.94	18.13
URR	0.28	0.75	0.52	0.096
Creatinine (mg/dl)	5.70	14.40	10.28	1.74
Na (mmol/L)	133.00	150.00	141.80	3.09
K (mmol/L)	3.50	5.10	4.38	0.34
Cholesterol (mg/dl)	78.00	305.00	158.20	54.64
LDL (mg/dl)	27.00	158.00	87.91	35.29
HDL (mg/dl)	21.00	60.00	37.77	9.43
Triglyceride (mg/dl)	48.00	400.00	171.75	79.03
Hb (g/dl)	6.40	14.50	10.29	1.66
Albumin (g/dl)	2.40	4.70	3.66	0.39
Alkaline phosphatase (IU)	57	684	207.22	176.90
Corrected Ca (mg/dl)	6.90	11.14	8.96	0.94
Phosphorus (mg/dl)	3.10	10.30	5.78	1.54
Ca Phosphorus product	25.40	94.50	51.62	14.06
iPTH (Pg/ml)	18.80	2500.00	813.68	610.91
Serum Iron (ug/dl)	39.00	170.00	76.5795	25.27
Transferrin Sat. %	9.90	74.50	32.53	12.24
Ferritin (ng/ml)	43.00	2990.00	670.00	559.92
Vascular Calcification Calcifications No (%) No calcifications No (%)	-	-	29 (33%) 59 (67%)	-
CCC Calcifications No (%) No calcifications No (%)	-	-	52 (59.1%) 36 (40.9%)	-

BMI: Body mass index, MBP: Mean blood pressure, URR: Urea reduction ratio, LDL: Low density lipoprotein, HDL: High density lipoprotein, Hb: Hemoglobin, Na: Sodium, K: Potassium, Ca: Calcium, iPTH: Intact Parathormone

Table 2: Comparison between patients with vascular calcification and those without calcifications

Variable	No vascular calcification (No 59, 67%)	Vascular calcifications (No 29, 33%)	Student t test/ Mann-Whitney test/ Chi square	*P* value
Age	50.03 ± 12.41	48.55 ± 12.79	0.5	>0.05
Sex F/M No (%)*	19(52.8%)/17(47.2%)	28(53.8%)/24(46.2%)	-	>0.05
Comorbidity*				>0.05
DM				
No	46 (78 %)	23 (79.3%)	1	>0.05
Yes	13 (22%)	6 (20.7%)		
HTN/CVD				
No	29 (49.2%)	13 (44.8%)	0.82	>0.05
Yes	30 (50.8%)	16 55.2%)		
Hepatitis C and B				
No	40 (67.8%)	21 (72.4)	0.81	>0.05
Yes	19 (32.2%)	8 (27.6%)		
Combined				
No	46 (78%)	23 (79.3%)	1	>0.05
Yes	13 (22%)	6 (20.7%0		
BMI	27.52 ± 3.64	26.86 ± 4.01	1.9	>0.05
MBP pre dialysis (mmHg)	106.02 ± 16.00	102.24 ± 12.88	1.1	>0.05
MBP post dialysis (mmHg)	87.46 ± 13.55	87.24 ± 12.76	1.3	>0.05
Duration of dialysis (Years)	5.58 ± 2.96	5.69 ± 3.18	0.16	>0.05
Urea reduction ratio	53.50 ± 10.08	50.28 ± 8.37	1.5	>0.05
Urea pre dialysis (mg/dl)	150.08 ± 40.07	155.83 ± 36.87	0.6	>0.05
Urea post dialysis (mg/dl)	68.07 ± 17.31	76.79 ± 18.65	2.2	0.04
Creatinine (mg/dl)	10.44 ± 1.79	9.95 ± 1.60	1.2	>0.05
Albumin (g/dl)	3.61 ± 0.40	3.77 ± 0.34	0.4	>0.05
Cholesterol (mg/dl)	157.69 ± 57.76	159.24 ± 48.64	0.12	>0.05
LDL (mg/dl)	86.93 ± 36.62	89.90 ± 32.95	0.36	>0.05
HDL (mg/dl)	36.75 ± 8.74	39.86 ± 10.54	1.5	>0.05
Triglyceride (mg/dl)	171.44 ± 78.21	172.38 ± 82.07	0.05	>0.05
Hb (gm/dl)	10.34 ± 1.73	10.20 ± 1.54	0.36	>0.05
Alkaline phosphatase (IU)#	194.90 ± 176.25	231.38 ± 179.12	0.90	>0.05
Corrected Ca (mg/dl)	9.06 ± 0.95	8.75 ± 0.90	1.5	>0.05
Phosphorus (mg/dl)	5.20 ± 1.19	6.95 ± 1.52	5.4	0.000
Ca Phosphorus product	47.06 ± 11.34	60.89 ± 14.66	4.8	0.000
iPTH (Pg/ml)#	673.54 ± 558.78	1098..80 ± 622.33	3.2	0.002
Na (mmol/L)	142.10 ± 2.48	141.17 ± 4.05	1.13	>0.05
K (mmol/L)	4.40 ± 0.33	4.36 ± 0.37	0.5	>0.05
Serum Iron (ug/dl)	73.61 ± 23.86	82.62 ± 27.37	1.5	>0.05
Ferritin (ng/ml)#	669.69 ± 574.98	670.62 ± 537.86	0.15	>0.05
Transferrin saturation %	31.34 ± 12.24	34.96 ± 12.08	1.3	>0.05

*: Chi square, #: Mann-Whitney test, F/M: Female/Male, DM: Diabetes mellitus, HTN/CVD: Hypertenssion/Cardiovascular disease, BMI: Body mass index, MBP: Mean blood pressure, LDL: Low density lipoprotein, HDL: High density lipoprotein, Ca: Calcium,iPTH: Intact Parathormone, Na: Sodium, K: Potassium

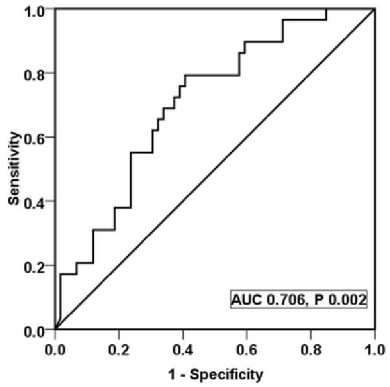

Figure 3: ROC curve to detect cut off value of iPTH for prediction of vascular calcification.
ROC: Receiving operation characteristics, iPTH: Intact parathormone,

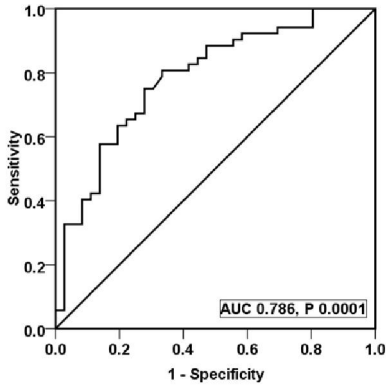

Figure 4: ROC curve to detect cut off value of iPTH for prediction of conjunctival and corneal calcification (CCC).
ROC: Receiving operation characteristics, iPTH: Intact parathormone, CCC: Conjunctival and corneal calcification

Table (3) Comparison between patients with corneal calcification and those without calcifications

Variable	No corneal calcification (No 36)	Corneal calcification (No 52)	Student t test/ Mann-Whitney test/ Chi square	*P* value
Age	51.61 ± 11.43	48.12 ± 13.07	1.3	>0.05
Sex F/MNo (%)*	30(50.8%)/29(49.2%)	17(58.6%)/12(41.4%)	-	>0.05
Comorbidity*				
DM				
No	25 (69.4%)	44 (84.6%)	0.12	>0.05
Yes	11 (30.6%)	8 (15.4%)		
HTN/CVD				
No	20 (55.6%)	22 (42.3%0	0.28	>0.05
Yes	16 (44.4)	30 (57.7%)		
Hepatitis C and B				
No	21 (58.3%)	40 (76.9)	0.09	>0.05
Yes	15 (41.7)	12 (23.1)		
Combined				
No	25 (69.4%)	44 (84.6%)	0.12	>0.05
Yes	11 (30.6%)	8 (15.4%)		
BMI	28.56 ± 2.93	25.87 ± 5.40	3.01	0.003
MBP pre dialysis (mmHg)	102.50 ± 13.90	106.35 ± 15.78	1.1	>0.05
MBP post dialysis (mmHg)	85.65 ± 11.79	88.59 ± 14.12	1.02	>0.05
Duration of dialysis (Years)	4.50 ±1.84	6.38 ± 3.42	3.34	0.001
Urea reduction ratio	51.63 ± 10.31	53.00 ± 9.17	0.4	>0.05
Urea predialysis (mg/dl)	144.06 ± 39.34	157.46 ± 38.05	1.6	>0.05
Urea postdialysis (mg/dl)	68.06 ± 18.36	72.94 ± 17.87	1.2	>0.05
Creatinine (mg/dl)	10.13 ± 1.59	10.38 ± 1.84	0.6	>0.05
Albumin (gm/dl)	3.58 ± 0.35	3.73 ± 0.41	2.4	>0.05
Cholesterol (mg/dl)	161.31 ± 58.31	156.06 ± 53.90	0.4	>0.05
LDL (mg/dl)	86.39 ± 34.18	88.96 ± 36.33	0.3	>0.05
HDL (mg/dl)	35.92 ± 10.80	39.06 ± 8.21	1.4	>0.05
Triglyceride (mg/dl)	174.75 ± 67.75	169.67 ± 86.57	0.7	>0.05
Hb (mg/dl)	10.63 ± 1.66	10.06 ± 1.64	1.5	>0.05
Alkaline phosphatase (IU)#	177.66 ± 152.89	225.08 ± 189.23	0.98	>0.05
Corrected Ca (mg/dl)	9.04 ± 0.94	8.91 ± 0.94	0.6	>0.05
Phosphorus (mg/dl)	4.80 ± 1.07	6.46 ± 1.45	5.8	0.0001
Ca Phosphorus product	43.33 ± 10.72	57.35 ± 13.28	5.2	0.0001
iPTH (Pg/ml)#	485.74 ± 471.73	1040.70 ± 596.22	4.6	0.003
Na (mmol/L)	141.94 ± 3.08	141.69 ± 3.13	0.3	>0.05
K (mmol/L)	4.39 ± 0.31	4.38 ± 0.36	0.2	>0.05
Serum Iron (ug/dl)	76.39 ± 22.62	76.71 ± 27.18	0.06	>0.05
Ferritin (ng/ml)#	643.72 ± 443.81	688.19 ± 611.24	0.6	>0.05
Transferrin saturation	33.56 ± 12.23	31.82 ± 12.31	0.6	>0.05

*: Chi square, #: Mann-Whitney test, F/M: Female/Male, DM: Diabetes mellitus, HTN/CVD: Hypertenssion/Cardiovascular disease, BMI: Body mass index, MBP: Mean blood pressure, LDL: Low density lipoprotein, HDL: High density lipoprotein, Ca: Calcium,iPTH: Intact Parathormone, Na: Sodium, K: Potassium

4. Discussion:

Vascular calcification is prevalent in hemodialysis patients and is associated with all-cause and cardiovascular mortality (8) Kidney Disease: Improving Global Outcomes (KDIGO) has recommended that a lateral abdominal radiograph and echocardiography should be used as appropriate alternatives to cardiac CT to detect vascular calcifications (9). The degree of abnormal soft tissue calcification progressed as degree of renal disease increased and can happened throughout the body in organs such as skin, eye, heart valve,myocardium, coronary arteries, lung, etc.(10). Ocular calcifications are the most common types of soft-tissue calcification seen in Stage 4 and 5 CKD and most of conjunctival calcium deposits are asymptomatic and. Slit-lamp examination permits easier recognition of these lesions (11). In our study we found that 29 (33 %) of 88 patients has vascular calcification as detected by lateral abdominal x ray for abdominal aorta. There are some reports that showed higher prevalence than our results. In one study included 40 hemodialysis patients identified calcification in abdominal aorta in 68 % of patients (12). Other reports showed calcification in abdominal aorta of 63.1 % (1), 65.4 % (13) and 81 % (14). The reported incidence of vascular calcification in dialysis patients has varied from 3% to 83% (11). In this study 52 (59.1 %) patients were found to have CCC out of 88 patients. Studies concerning the CCC have shown variable results. In concordance with our results Nasri H. et al founded 50 % with typical CCC in 24 hemodialysis patients (15). Other reports showed CCC prevalence of 79 % (5), 14 % (16), 87.3 % (6) and 24.1 % (17). Comparison between patients with vascular calcification and those without vascular

calcifications showed that serum phosphorus, Ca x P, urea post dialysis and iPTH were significantly higher in hemodialysis patients with vascular calcification. On the other hand our results did not show any significant difference among the two groups regarding age, duration of dialysis, serum calcium or comorbidities. Regression analysis and ROC curve demonstrated that iPTH was the predictor of vascular calcification with cut off value of 702 Pg/ml and AUC of 0.706. In accordance with our results Nafie et al found that vascular calcification has no relation to age and serum calcium and it related to iPTH, Phosphorus andCa x P, however in contrary to our results they showed that vascular calcification is related to duration of dialysis (18). Suzuke et al.,demonstrated that vascular calcification is related to iPTH (19). Pencak et al., found that there was no significant difference regarding serum phosphorus and Ca x P and the only predictor of abdominal aorta calcification is the age (20). Also Nitta et al.,could not find any relation of vascular calcification with calcium, phosphorus and iPTH (21). Our study was in contrast with Stephanie et al.,who showed that age and dialysis duration were associated with presence of vascular calcification (22).In our study the cohort was divided again according CCC. Comparison between patients with CCC and those without CCC showed that there was a significant difference between the two groups regarding serum phosphorus, Ca x P, iPTH, BMI and duration of dialysis. On the other hand there was not any significant difference between the two groups regarding age, serum calcium and comorbidities. Regression analysis and ROC curve demonstrated that iPTH is the only predictor of CCC with cut off value of 533 Pg/ml and AUC of 0.786.Similar to our results Tokuyama et al.,showed that CCC related to serum phosphorus, iPTH, Ca x P and duration of dialysis and there was no relation between CCC with age and serum calcium (5). Seyahi et al.,found a good relation of CCC with duration of renal replacement therapy, phosphorus and Ca x P however in contrast to our result he did not find relation of CCC with iPTH (6). Vrabec et al.,found that no correlation between CCC with iPTH and Ca x P and this study showed that Soft tissue calcifications in hemodialysis patients are often seen, moreover due to increasing age (16). In our study vascular calcifications as regard abdominal aortic calcifications were presented in 29 patients (33%). Out of 29 patients with Vascular calcifications 21 patients had CCC (72.4%). It means that CCC is highly associated with vascular calcification. In this study CCC were found in 52 (59.1%) patients. Out of 52 patients, 21 (40 %) showed vascular calcifications. It means vascular calcification is not associated with CCC. In our study iPTH was the predictor of both vascular and CCC with cut off value for prediction of 702 pg/ml and 533 pg/ml respectively. As the CCC was found in 52 (59.1%) patients more than vascular calcification 29 (33 %) and as CCC is highly associated with vascular calcification, however the vascular calcification is not associated with CCC and the cut off value of CCC is lower than that of vascular calcifications we can conclude that CCC may precede the occurrence of vascular calcification. There are some limitations of this study, first the small number of patients, second, it is an observational study and did not address the underlying mechanisms of vascular and CCC, third we did not follow up the patients to see if there is any regression of either vascular calcifications or CCC after lowering the iPTH levels.

Conclusion

Vascular calcifications and soft tissue calcification as CCC are highly prevalent in hemodialysis patients. iPTH was found to be the predictor of vascular calcification and CCC however with less cut off value (533 pg/ml) for CCC compared to vascular calcification (702 pg/ml). CCC may precede the occurrence of vascular calcification and attention should be paid for early diagnosis of soft tissue calcification. Simple test like slit lamp examination for detection of CCC should be recommended for hemodialysis patient and if CCC was found it should be considered as warning sign for occurrence of vascular calcifications. Levels of iPTH should not exceed 500 pg/ml in hemodialysis patients. Also we recommend a meta-analysis study to confirm our results and assess other sites for soft tissue calcifications and also to see the effect of more control and reduction of iPTH level on regression of both vascular and corneal calcifications.

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