Preoperative Calcium-Phosphorus Status and Arteriovenous Fistula Maturation

🕲 Cihan Uysal¹, 🕲 Hasan Çifçi², 🕲 Duygu Gören², 🕲 Rifat Özmen³, 🕲 İsmail Koçyiğit⁴

¹Ağrı Training and Research Hospital, Clinic of Nephrology, Ağrı, Türkiye ²Erciyes University Faculty of Medicine, Department of Internal Medicine, Kayseri, Türkiye ³Erciyes University Faculty of Medicine, Department of Cardiovascular Surgery, Kayseri, Türkiye ⁴Erciyes University Faculty of Medicine, Department of Nephrology, Kayseri, Türkiye

ABSTRACT

Introduction: Although arteriovenous fistula (AVF) is the preferred vascular access in hemodialysis (HD) practice, AVF maturation is a common issue. The current study investigated the possible role of preoperative serum calcium/phosphate levels in predicting AVF maturation.

Methods: Only patients with end-stage kidney disease who were candidates for chronic HD were included. The key inclusion criterion was having a newly created radiocephalic AVF. Patients who started chronic HD before AVF operation were excluded. A mature AVF was defined as blood flow >500 mL/minute and an access (cephalic) vein diameter >5 mm at 6 to 8 weeks post-operation, in ultrasonography.

Results: A total of 79 patients were included, with a median age of 62.4 years. AVF maturation was identified in 50 patients (63.3%). Serum calcium level was $8.9\pm0.6 \text{ mg/dL}$ in patients with mature AVF and $8.6\pm0.5 \text{ mg/dL}$ in patients with immature AVF (p=0.03). Hypocalcemia was more frequent (31.0% compared to 16%) in patients with immature AVF, whereas it was not statistically significant (p=0.117). A positive correlation was identified between serum calcium levels and cephalic vein diameters (p=0.012). Serum phosphate, parathyroid hormone, and calcium phosphate product were not significantly different between the two groups. Logistic regression analysis revealed that serum calcium level was an independent predictor for AVF maturation (p=0.035). In receiver operating characteristic analysis, sensitivity and specificity of calcium level (cut-off >8.7 mg/dL) were 70.0% and 59.6%, respectively, with an area under the curve of 0.65 (95% confidence interval 52.4-77.6, p=0.027).

Conclusion: Understanding the impact of preoperative calcium levels on AVF maturation may guide clinicians in optimizing biochemical parameters preoperatively, thus enhancing fistula success rates.

Keywords: Arteriovenous fistula, maturation, calcium, hypocalcemia, hemodialysis

Introduction

In chronic hemodialysis (HD) practice, arteriovenous fistula (AVF) is the preferred vascular access option. A mature AVF should have several features such as sufficient blood flow, a straight and adequate segment for cannulation, and be able to be cannulated repeatedly. Unfortunately, even with a successful operation, maturation presents a challenge for AVF utilization. Inadequate dilatation and early stenosis are among the frequent causes of AVF maturation failure (1). Clinicians should identify which potential risk factors are most relevant to fistula development in patients awaiting vascular access creation (2).

In normal physiological conditions, parathyroid hormone (PTH) stimulates osteoclast activity, resulting in the resorption of calcium and phosphorus from the bone. PTH also promotes the activation of vitamin

D in the kidneys. Active vitamin D enhances the absorption of calcium and phosphorus from the gastrointestinal tract and kidney tubules (3). However, calcium and bone metabolism are impaired in chronic kidney disease (CKD). Increased PTH and phosphate levels, with decreased calcium levels, are the main laboratory findings.

CKD-mineral and bone disorder (MBD) is a broad term for these disturbances and is not limited to secondary hyperparathyroidism. Phosphate retention, along with decreased glomerular filtration, essentially triggers this pathological process (4). The underlying mechanisms of CKD-MBD are complicated, involving intricate feedback loops between the kidneys, parathyroid glands, bones, intestines, and vasculature (5). The current study examined the AVF maturation problem, regarding calcium-phosphorus metabolism parameters.



Address for Correspondence: Cihan Uysal MD, Ağrı Training and Research Hospital, Clinic of Nephrology, Ağrı, Türkiye E-mail: drcihanuysal@hotmail.com ORCID ID: orcid.org/0000-0002-6214-0354

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Methods

This clinical investigation was carried out in accordance with the Helsinki Declaration. The procedure of the study was explained to the patients to obtain written informed consent. This study was conducted as a single-center, observational study. This study has been approved by the Erciyes University Health Sciences Research Ethics Committee (approval number: 2024/269, date: 04.12.2024).

Study Design

This retrospective study was conducted in a single center. The patient screening period was limited to two years from 01/2023 to 12/2024. The key inclusion criterion was having a newly created AVF for chronic HD treatment and subsequently being assessed by ultrasonography (USG) for AVF maturation. Only adult patients with radiocephalic fistula were enrolled. Patients undergoing chronic HD before AVF operation were excluded. Patients with an AVF that was non-functioning shortly after the operation were excluded. Also, patients were not excluded if a dialysis catheter was concurrently inserted during the operation due to immediate HD indications.

Arteriovenous Fistula Maturation Assessment

Maturation was identified by USG at 6-8 weeks after the AVF operation. The access vessel (cephalic vein) diameter, the feeding artery (radial artery) diameter, and the fistula blood flow rate (5 cm proximal to the anastomosis) were measured by Duplex USG. A mature AVF was defined as a cephalic vein diameter >5 mm and a fistula blood flow >500 mL/ minute (min).

Laboratory Assessment

Preoperative laboratory results were used in analyses. Total serum calcium measurement was corrected according to the serum albumin. Corrected calcium (mg/dL) was calculated using the following formula. Measured total calcium (mg/dL) + $0.8 \times [4.0 - \text{serum albumin (g/dL)}]$. Hypocalcemia was defined as a total serum calcium concentration below 8.5 mg/dL, and hyperphosphatemia was defined as a serum phosphate concentration above 4.5 mg/dL.

Statistical Analysis

Histograms and q-q plots were examined, and the Shapiro-Wilk test was performed to assess the normality of the data. Levene's test was applied to test variance homogeneity. To compare the differences between groups, either a two-sided Independent samples t-test or Mann-Whitney U test was used for continuous variables, or Pearson's χ^2 analysis or Fisher's exact test was used for categorical variables. The Spearman correlation coefficient was used to explore the relationship between numerical variables. Binary logistic regression analyses were performed to identify the risk factors for progression. Predicted probabilities of each model were included in receiver operating characteristic (ROC) curve analysis to identify and compare the predictive performances of the models. Analysis was conducted using R 4.2.3 (http://www.r-project.org) and EasyROC software. A p-value less than 5% was considered statistically significant.

Results

In this study, a total of 79 patients were analyzed. The mean age of patients was 62.4 ± 11.8 years. Sixty-nine patients (87.3%) underwent only an AVF creation as a first HD access. Dialysis catheter insertion concurrently with AVF creation was performed in 10 patients (12.7%, 12.7) due to urgent dialysis indications.

Diabetes mellitus (DM) was diagnosed in 29 patients (36.7%) and was the most common primary cause of CKD in our cohort. Hypertension (HT) ranked as the second most prevalent primary cause of CKD (26.6%), although HT was diagnosed in 55 patients (69.6%). Peripheral vascular disease (PVD) was identified in 5 patients (6.3%) as a comorbidity.

Mature AVF was identified in 50 patients (63.3%). The median fistula blood flow was 685.0 (622.0-750.0) mL/min in patients with mature AVF and 180.0 (130.0-250.0) mL/min in patients with non-maturing AVF. The mean access vessel (cephalic vein) diameter was 5.2 (4.6-5.7) mm in patients with mature AVF, and 2.8 (1.7-3.6) mm in patients with non-maturing AVF. The median radial artery diameter was 4.1 (3.6-4.6) mm in patients with mature AVF, and 2.3 (2.0-3.0) mm in patients with non-maturing AVF.

The mean age was 59.4 ± 12.1 in patients with mature AVF and 67.5 ± 9.5 in patients with non-maturing AVF. Also, age was statistically significantly higher in patients with non-maturing AVF (p=0.002). Laboratory parameters were analyzed according to AVF maturation groups. There were no statistically significant differences in blood urea nitrogen, creatinine, sodium, potassium, uric acid, protein, albumin, aspartate aminotransferase, alanine aminotransferase, leukocyte, or hemoglobin levels between the two groups. The results are summarized in Table 1.

Two AVF maturation groups were analyzed according to the presence of DM. AVF immaturity rate was 58.6% in diabetic patients, whereas it was 24.0% in non-diabetic patients. The frequency of non-maturing AVF was statistically significantly higher in diabetic patients (p=0.002).

Two AVF maturation groups were analyzed according to the presence of HT. AVF maturation rate was 60.0% in hypertensive patients, whereas it was 70.8% in non-hypertensive patients. The frequency of maturing AVF was not significantly higher in diabetic patients (p=0.255).

Only four patients used calcium-containing phosphate binders, so we did not analyze these patients based on AVF maturation status. Additionally, 20 patients (25.3%) used oral calcitriol (active vitamin D) medication. No association was found between AVF maturation and whether patients used calcitriol (p=0.124).

The average total serum calcium level was $8.8\pm0.6 \text{ mg/dL}$ in all patients, and the hypocalcemia frequency was 21.5% (n=17). Serum total calcium level was statistically significantly higher in patients with mature AVF ($8.9\pm0.6 \text{ mg/dL}$) than in those with non-maturing AVF ($8.6\pm0.5 \text{ mg/dL}$). The results are summarized in Table 2.

The frequency of hypocalcemia was 16.0% (n=8) in patients with mature AVF, and 31.0% (n=9) in patients with non-maturing AVF. Despite the higher frequency of hypocalcemia in patients with non-maturing AVF, it was not statistically significant (p=0.117).

The average serum phosphate level was 4.1 \pm 1.0 mg/dL in all patients, with hyperphosphatemia occurring in 29.1% (n=23). Serum phosphate level was 4.1 \pm 1.1 mg/dL in patients with mature AVF, 4.2 \pm 0.8 mg/dL in patients with non-maturing AVF, and a statistically significant difference was not determined (p=0.364). The frequency of hyperphosphatemia was 30.0% (n=15) in patients with mature AVF and 27.6% (n=8) in patients with non-maturing AVF. Despite the higher frequency of hyperphosphatemia in patients with mature AVF, it was not statistically significant (p=0.820).

The average calcium phosphate product (CaxP) value was 35.9 ± 11.1 mg²/dL² in patients with mature AVF, and 36.9 ± 8.5 mg²/dL² in patients with non-maturing AVF. There was no statistically significant difference in CaxP values between the two AVF maturation groups (p=0.684).

The median PTH level was 207 (93.5-281.5) pg/mL in patients with mature AVF, and 242 (93.5-281.5) pg/mL in patients with non-maturing AVF. There was no statistically significant difference in serum PTH levels between the two AVF maturation groups (p=0.655).

No correlation was identified between serum calcium levels and fistula blood flows (p=0.123), as shown in Figure 1. However, a positive correlation was identified between serum calcium levels and cephalic vein diameters (p=0.012), as shown in Figure 2. Serum phosphate levels were not correlated with fistula blood flows (p=0.878) and cephalic vein diameters (p=0.343). CaxP values and PTH levels were not correlated with fistula blood flows or cephalic vein diameters.

Binary logistic regression analysis identified two independent predictors of AVF maturation: serum calcium level (p=0.035) and age (p=0.006). The results are summarized in Table 2.

Serum calcium levels significantly predicted AVF maturation in ROC analysis. The sensitivity and specificity of calcium level were 70.0% and 59.6% (cut-off >8.7 mg/dL) with an area under the ROC curve of 0.65, (95% confidence interval 52.4-77.6, p=0.027). The results are summarized in Table 3, and the ROC diagram is shown in Figure 3.

Table 1. comparison of the patients according to AVT maturation status						
Parameters	Mature AVF (n=50)	Immature AVF (n=29)	р			
Age (years)	59.4±12.1	67.5±9.5	0.002			
BMI (kg/m ²)	24.4 (22.4-28.4)	25.5 (22.4-29.3)	0.855			
Glucose (mg/dL)	108 (93-167)	120 (102-166)	0.234			
BUN (mg/dL)	41 (37-64)	48 (29-45)	0.134			
Creatinine (mg/dL)	4.7 (3.6-6.1)	3.7 (3.3-5.1)	0.085			
Uric acid (mg/dL)	5.7±1.8	5.7±2.1	0.994			
Sodium (mmol/L)	137.8±3.7	137.9±2.4	0.832			
Potassium (mmol/L)	4.3 (4.1-5.0)	4.4 (4.0-5.0)	0.780			
Protein (g/dL)	6.4±0.7	6.7±0.8	0.166			
Albumin (g/dL)	3.8 (3.4-4.2)	3.8 (3.2-4.0)	0.684			
Calcium (mg/dL)	8.94±0.63	8.62±0.58	0.030			
Phosphate (mg/dL)	4.11±1.12	4.20±0.85	0.364			
CaxP (mg ² /dL ²)	35.9±11.1	36.9±8.5	0.684			
PTH (pg/mL)	207 (93.5-281.5)	242 (93.5-281.5)	0.655			
Hemoglobin (g/dL)	10.6±1.7	10.5±1.7	0.679			
Leukocyte (cell/µL)	7.4±2.4	8.2±2.3	0.163			
Platelet (10 ³ /µL)	222 (192-275)	213 (171-309)	0.383			

Table 1. Comparison of the patients according to AVF maturation status

Values are expressed as mean ± standard deviation, median (1st-3rd quartiles), AVF: Arteriovenous fistula, BUN: Blood urea nitrogen, BMI: Body mass index, CaxP: Calcium phosphate product, PTH: Parathyroid hormone

Table 2. The results of binary	logistic regression analysis
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Table 2. The results of binary logistic regression analysis						
Parameters	β	HR	95% CI	р		
Age	-0.077	0.926	0.878-0.977	0.005*		
BUN	0.330	1,033	0.993-1,075	0.106		
Creatinine	0.049	1,051	0.781-1,413	0.745		
Protein	0.377	1,459	0.428-4,970	0.546		
Glucose	-0.002	0.998	0.989-1,006	0.605		
Calcium	0.927	2,528	1,069-5,977	0.035*		
Phosphate	-0.457	0.633	0.055-7,359	0.715		
CaxP	0.005	1,005	0.755-1,337	0.937		
PTH	0.001	1,001	0.998-1,003	0.651		

HR: Hazard ratio, CI: Confidence interval, PTH: Parathyroid hormone, BMI: Body mass index, CaxP: Calcium phosphate product, BUN: Blood urea nitrogen



Figure 1. The correlation analysis of calcium levels and fistula blood flows is shown in the scatter plot



Figure 2. The correlation analysis between calcium levels and access vein diameters is shown in a scatter plot

Table 3. The results of ROC analysis							
ROC statistics			Diagnostic statistics				
Parameter	AUC (95% CI)	р	SEN (95% CI)	SPE (95% CI)	PPV (95% CI)	NPV (95% CI)	
Calcium (>8.7 mg/dL)	65.0 (52.4-77.6)	0.027	70.0 (46.5-92.5)	59.6 (38.9-76.5)	70.6 (54.6-87.7)	48.3 (31.3-74.8)	

AUC: Area under the curve, ROC: Receiver operating characteristic, CI: Confidental interval, SEN: Sensitivity, SPE: Specificity, PPV: Positive predictive value, NPV: Negative predictive value



Figure 3. The predictor power of parameters for AVF maturation with ROC curve

AVF: Arteriovenous fistula, ROC: Receiver operating characteristics, CaxP: Calcium phosphate product

Discussion

HD efficacy first depends on sufficient vascular access. Therefore, vascular access was described as the Achilles' heel of HD in clinical practice. AVF is the preferred vascular route in HD practice. Long-term patency and lower complication risk make it stand out. However, maturation failure was an undesired result of the AVF creation.

In this study, we have focused on the possible impact of calcium and phosphate metabolism on AVF maturation in pre-dialysis CKD patients. We analyzed these two clinical situations from different perspectives. Serum calcium concentration, serum phosphate concentration, CaxP value, PTH, hypocalcemia status, and hyperphosphatemia status were among the utilized parameters in analyses. Maturation status, vessel diameters, and fistula blood flow were analyzed in vascular access evaluation.

First, we identified significantly higher serum calcium levels in patients with mature AVF than in patients with immature AVF. Nevertheless, hypocalcemia frequency was higher in patients with immature AVF, but it was not statistically significant. Lastly, we determined a positive correlation between serum calcium levels and cephalic vein diameters. However, no relevance was not identified between serum phosphate or CaxP and AVF maturation.

In this study design, we imposed several limitations in patient selection. Patients with a radiocephalic AVF location should be in the predialysis period. Only one location option was used to minimize anatomic risk factors. Previous studies reported distinct AVF locations with different maturation rates. Additionally, undergoing dialysis has been reported as a factor affecting AVF maturation. In addition, long-term dialysis history has been associated with deterioration of the vascular structure. This elimination was preferred because the variability in dialysis durations among patients could significantly influence the results.

However, a review of the literature revealed that studies investigating AVF maturation predominantly focused on patients undergoing HD treatment (2,6). From this standpoint, we believe the current findings offer significant value.

Both the presence of DM and advanced age were associated with poor outcomes in the AVF maturation process in our cohort. We determined a statistically higher frequency of immature AVF (58.6%) in diabetic participants. In fact, the mentioned results were also, consistent with the literature. DM was reported as a significant negative predictor of venous remodeling in dialysis patients. DM can lead to a pro-thrombotic state, endothelial injury, and extracellular matrix expansion on vasculature (7). The mentioned alterations could contribute to thrombosis and stenosis in AVF. The outcomes of numerous studies show that elderly patients with radiocephalic AVF had increased primary failure rates and decreased patency (8).

In our cohort, the presence or absence of HT was not associated with AVF maturation. Furthermore, the frequency of PVD among our patients was quite low (5 patients). This may be related to the study design, because only patients with radiocephalic AVF were included, excluding primarily non-functioning fistulas. Therefore, we could not analyze the effect of PVD on AVF maturation.

In CKD, the clinical importance of hypocalcemia and hyperphosphatemia extends beyond electrolyte imbalance. These disturbances are associated with poor clinical outcomes and are closely linked with increased mortality in CKD. Despite these electrolyte disturbances being separate entities, they are also components of the main clinical condition defined as CKD-MBD. The cardiovascular system is severely affected by these electrolyte disturbances. Hypocalcemia is an independent predictive factor for cardiac dysfunction in patients with CKD (9). Increased phosphate levels induce HT, vascular calcification, cardiac valvular calcification, atherosclerosis, left ventricular hypertrophy, and myocardial fibrosis in CKD (10). Furthermore, CaxP is a clinically relevant tool in CKD to estimate the vascular risk of patients (11).

A high frequency of hypocalcemia (21.5%) was determined, and only 66.4% of individuals diagnosed with hypocalcemia used calcitriol serum calcium levels should be corrected with medications during the predialysis period, as well as during the dialysis period in CKD patients. It is probably overlooked because most cases are asymptomatic. However, our findings highlight the differential importance of hypocalcemia and the implications of its management. In the advanced stages of CKD, KDIGO guidelines recommend monitoring for serum calcium and phosphate every 1-3 months and targeting normal serum calcium levels (5).

Although AVF is the most preferred type of vascular access, the increased AVF failure rate has been remarkable in recent years (12). Identifying risk factors for AVF failure in advance may provide therapeutic benefits. An accomplished AVF maturation requires functional and structural adaptations in the inflow artery and outflow vein. The physiology of the AVF maturation process is complicated and largely unclear. The blood is shunted into the vein after AVF creation and the increased blood flow leads to vein remodeling. The increased blood flow results in augmented vessel wall shear stress and induces vasodilation in the vein.

Nitrous oxide and matrix metalloproteinases are essential in this step (13). The main cause of maturation failure is an anatomic problem, such as vascular stenosis (14).

We analyzed the preoperative status of the two amenable electrolytes in the AVF maturation process. Hypocalcemia could emerge through distinct mechanisms in CKD, such as vitamin D deficiency and hyperphosphatemia. Hypocalcemia typically does not occur until eGFR <15 mL/min. In one study, the frequency of hypocalcemia was reported as 23.6% in patients with advanced CKD (15). The hypocalcemia frequency was found to be 21.5% in our results, and this rate was consistent with existing literature.

In previous studies, we encountered confusing results about the relationship between serum calcium concentration and AVF maturity. Kubiak et al. (16) reported that serum mineral concentrations were not associated with major histological characteristics of veins or AVF maturation failure. However, Moon et al. (17) identified hyperphosphatemia as an indicator of AVF maturation failure and shortened AVF patency in dialysis patients. In another study, high CaxP values were associated with an increased risk of AVF failure by causing arterial stiffness in dialysis patients (18). Furthermore, higher serum PTH levels lead to an increase in the risk of AVF maturation failure through the transition of vascular smooth muscle cells to myofibroblasts (19). On the contrary, Masengu et al. (20) reported that arterial stiffness (measured by invasive methods) was not associated with AVF maturation.

The underlying explanation for the current results remains unclear. However, it can be hypothesized that the smooth muscle cell layer in the vessel wall may be influenced by serum calcium levels during the vessel dilatation phase. Calcium ions are known to be essential for smooth muscle function (21). Moreover, decreased calcium levels are both an indicator and a component of CKD-MBD, which is a recognized risk factor for VC. Also, VC could impede the adequate dilatation of the feeding artery, a process essential for successful AVF maturation. Nevertheless, the outcomes related to serum phosphate levels appear inconsistent with the literature, potentially because our laboratory data were obtained during the pre-dialysis period. Additionally, phosphorus levels in our study were not markedly elevated, with an average serum phosphate concentration of 4.1 mg/dL, which is within the normal range. It is worth noting that the majority of existing studies have been conducted in populations undergoing maintenance HD (6).

Study Limitations

Firstly, several laboratory parameters could be added to the analysis, such as 25-dihydroxyvitamin D level, alkaline phosphatase, and FGF-23 level. Increased patient numbers ensure more accurate results, although it's worth noting that similar studies in the literature have reported comparable patient numbers. Another limitation is the absence of CKD-MBD treatment, such as phosphate binders or calcitriol.

Conclusion

Although numerous risk factors for AVF maturation failure have been identified, we underscored an amenable factor. Maintaining optimal serum calcium levels should be considered a potential contributor to improving AVF patency in patients scheduled for HD.

Ethics

Ethics Committee Approval: This study has been approved by the Erciyes University Health Sciences Research Ethics Committee (approval number: 2024/269, date: 04.12.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions: Surgical and Medical Practices - R.Ö., İ.K.; Concept - C.U., R.Ö., İ.K.; Design - C.U., R.Ö., İ.K.; Data Collection or Processing - H.Ç., D.G.; Analysis or Interpretation - C.U., H.Ç., R.Ö., İ.K.; Literature Search - C.U., D.G., R.Ö., İ.K.; Writing - C.U., H.C., D.G., R.Ö.

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