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TANAFFOS

Role of Calcium Levels in Ventilatory Efficiency and Cardiopulmonary Function in Chronic Kidney Disease Patients

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Background: Exercise intolerance is common in patients with chronic kidney disease (CKD) and may reflect abnormalities in cardiovascular function, skeletal muscle performance, and metabolic regulation. This study investigated the associations between selected biochemical parameters and cardiopulmonary function in adults with non-dialysis CKD stages 3–5.

Materials and Methods: This observational cross-sectional study included 80 adults with non-dialysis chronic kidney disease (CKD) stages 3–5. Demographic characteristics, clinical history, laboratory measurements, and cardiopulmonary exercise testing (CPET) parameters were assessed. Logistic regression analyses were performed to investigate factors associated with increased ventilatory demand during exercise, and receiver operating characteristic (ROC) analyses were used to evaluate the discriminatory performance of selected biochemical parameters.

Results: The study population was predominantly male (62.5%), with a mean age of 42 years. The univariable analysis identified that only the mean serum vitamin D differed among the various serum calcium levels (P<0.001). Specifically, individuals with calcium levels ≥ 8.6 mg/dL (P=0.009) and those with calcium levels ranging from 8 to 8.6 mg/dL (P=0.001) had lower mean vitamin D levels compared to individuals with calcium levels ≤ 8 mg/dL. In the final multivariable model, it was found that only serum calcium levels had a statistically significant association with increased ventilation demand during exercise (VE/VCO_2 >35 L/min**)**. Specifically, patients with serum calcium levels ≥ 8.6 mg/dL had approximately 7 times higher odds of increased ventilation demand (VE/VCO_2 >35 L/min**)** compared to those with calcium levels ≤ 8 mg/dL (P=0.041).

Conclusion: This study underscores the intricate interplay between biochemical markers and cardiopulmonary health in CKD patients, providing insights into exercise intolerance. Serum calcium levels may hold diagnostic value, warranting further investigation into their clinical utility.

Keywords: Renal insufficiency; Cardiopulmonary function; Ventilatory efficiency; Calcium

INTRODUCTION

Chronic kidney disease (CKD) is a pervasive health concern, silently affecting the lives of approximately one in seven adults in the United States (1). While CKD's impact is profound and far-reaching, one of the most insidious symptoms it manifests is exercise intolerance, a

phenomenon that impedes individuals even during routine, low-intensity activities (2). This issue is of paramount importance, as it not only diminishes the quality of life for CKD patients but also significantly heightens their susceptibility to various medical complications, ultimately becoming a predictor of morbidity and mortality within this patient cohort. The complex interplay among central and peripheral factors and underlying disorders that contribute to exercise intolerance in CKD remains only partially understood (2-7). However, a better understanding of the underlying physiological mechanisms may facilitate the development of targeted interventions to improve pulmonary function and enhance the quality of life of patients with CKD.

In addition to the challenge of exercise intolerance, CKD patients face an elevated risk of mortality from various diseases (1). Therefore, early identification of subclinical abnormalities that may predispose individuals to cardiovascular complications is essential, as it enables timely interventions that may mitigate disease progression and improve cardiovascular outcomes.

The emergence of the cardiopulmonary exercise test presents a promising tool in the clinical arsenal, offering a novel approach to diagnose, assess, and evaluate the response to treatment in CKD patients (8). Furthermore, this test serves as a therapeutic avenue for dissecting the intricate mechanisms responsible for exercise intolerance (9). Notably, beginning at stage 3 of CKD, patients experience perturbations in calcium and phosphorus metabolism, coupled with aberrations in vitamin D levels, fibroblast growth factor 23 (FGF23), and parathyroid hormone (PTH), which collectively lead to vascular calcification and endothelial dysfunction (10, 11). These disturbances significantly impact physical activity tolerance and the diagnosis of pulmonary conditions, further eroding the patient's quality of life.

This study endeavors to shed light on the calcium and phosphorus disorders in CKD patients with exercise intolerance through the prism of cardiopulmonary exercise testing. By identifying optimal thresholds at each CKD stage, we aim to harness the power of phosphorus management to enhance daily activity tolerance and reduce the burden of cardiopulmonary diseases stemming from prolonged inactivity in this vulnerable patient group. In doing so, we aspire to unlock new avenues for improving the health and well-being of CKD patients, fostering hope for a brighter and healthier future.

MATERIALS AND METHODS

Study Design

This cross-sectional study aimed to investigate the association between cardiopulmonary exercise test (CPET) parameters and calcium–phosphorus metabolism disorders in patients with stages 3–5 chronic kidney disease (CKD) who were not receiving dialysis. The study was conducted at the chronic kidney disease clinic of Shahid Labbafinezhad Hospital and included adult patients aged ≥18 years.

Study Population

The study community comprised non-dialysis chronic kidney disease patients at stages 3 to 5. Inclusion criteria encompassed individuals with a glomerular filtration rate (GFR) below 60 mL per minute based on body surface area and who were over 18 years old. Patients were required to provide informed consent to participate in the study. GFR was calculated for all patients using the CKD-EPI method to determine their stage of chronic kidney disease. Patients meeting any of the following criteria were excluded from the study: Inability to walk independently or the presence of absolute contraindications for cardiopulmonary exercise testing. Hemoglobin levels below 9 g/dL. Uncontrolled blood pressure. Active and untreated coronary disease. A history of coronary heart disease was studied to assess cardiopulmonary exercise test performance before the development of coronary artery disease in chronic kidney failure patients.

Data Collection

Cardiopulmonary exercise tests were conducted free of charge on-site using a limited graded symptom approach. Patients were instructed to avoid heavy exercise and

caffeine consumption within 24 hours before the test and to continue their regular medication regimen. In addition to the cardiopulmonary exercise test, laboratory measurements included: 1) Serum albumin, 2) Serum calcium, 3) Serum phosphorus, 4) Serum vitamin D3, and 5) Serum creatinine. Calcium and phosphorus measurements for bone metabolic status were based on the average levels observed in patients over 3 to 6 months.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 21.0). Descriptive analyses were initially conducted to summarize the demographic and clinical characteristics of the study population and the distribution of key variables. The results are presented using appropriate tables and figures.

Subsequently, both univariable and multivariable logistic regression analyses were applied to investigate the intricate relationship between the measured laboratory parameters and exercise intolerance in patients with chronic kidney failure stages 3 to 5. Univariable logistic regression dissected the impact of individual variables in isolation, shedding light on their potential role as predictors of exercise limitations. In contrast, multivariable logistic regression models were employed to account for potential confounders by simultaneously considering multiple variables. This approach allowed for the identification of factors that independently contributed to exercise intolerance while controlling for other relevant variables. Lastly, Receiver Operating Characteristic (ROC) curves were generated for serum calcium, phosphorus, and the calcium-phosphorus product, aiding in the determination of optimal cutoff values that effectively discriminated between patients with and without exercise intolerance at different CKD stages.

Laboratory Measurements

The following laboratory measurements were conducted for all study participants. Serum albumin levels were determined using standard laboratory techniques. A cutoff value of less than 3.5 g/dL was considered abnormal. Serum calcium levels were measured using standard methods, and values below 8.4 mg/dL were considered below the normal range. Serum phosphorus levels were assessed using established laboratory procedures. Levels exceeding 4.5 mg/dL were considered above the normal range. Vitamin D3 levels were determined through laboratory analysis, with values below 30 ng/mL considered insufficient. Serum creatinine was measured as a marker of kidney function, and values above 1.2 mg/dL in females and above 1.4 mg/dL in males were considered elevated.

During the cardiopulmonary exercise test (CPET), various parameters related to cardiorespiratory function were assessed. The following CPET parameters and their respective cutoff values were utilized to evaluate exercise intolerance and cardiorespiratory function: The PET CO_2 value provides insights into ventilation-perfusion matching and respiratory efficiency during exercise. The normal range for PET CO_2 is typically considered to be 35-40 mmHg. Values below 35 mmHg may indicate inefficient ventilation or impaired pulmonary function. VE/VCO_2 (Ventilation/Carbon Dioxide Production) represents the ventilatory efficiency of the lungs. A VE/VCO_2 value below 35 is considered normal, while values above this cutoff may indicate increased ventilatory demands during exercise. VE/VO_2 (Ventilation/Oxygen Consumption) is another indicator of ventilatory efficiency, reflecting the ratio of ventilation to oxygen consumption. A VE/VO_2 value below 32 is generally considered within the normal range, while values exceeding this cutoff may suggest ventilatory inefficiency during exercise.

Ethics Approval and consent to participate

This research received ethical approval from the ethics committee of Shahid Beheshti University of Medical Sciences, with the assigned ethics code (IR.SBMU.MSP.REC.1398.766). The study was also registered in clinicaltrials.gov under the identifier NCT04013139. Strict adherence to ethical principles was maintained throughout the study to protect the rights and well-being of the study participants. We extracted data from the dataset, and the IRB classified the study as minimal risk research because we waived the need for participant informed consent.

RESULTS

In this study, 80 patients with chronic kidney disease were examined. The overall mean age of the patients was 41.96 ± 10.74 years, with 62.50% of the patients being male. The most common underlying diseases in these patients were hypertension (40%), diabetes (28.75%), and dyslipidemia (10%).

After examining the clinical factors in these patients, it was observed that the overall mean serum calcium level was 8.35 ± 0.52 mg/dL. Upon reviewing the serum calcium levels, it was found that 31.25% of the patients had calcium levels ≤ 8 mg/dL (n=25), 46.25% had calcium levels in the range of 8 to 8.6 mg/dL (n=37), and 22.50% had serum calcium levels ≥ 8.6 mg/dL (n=18).

After examining and comparing the demographic and hemodynamic characteristics, as well as the clinical and medication history of the patients, no statistically significant differences were observed among the mentioned factors at different serum calcium levels (P>0.05). However, upon reviewing the laboratory parameters, it was found that only the mean serum vitamin D differed among the various serum calcium levels (P<0.001). Specifically, individuals with calcium levels ≥ 8.6 mg/dL (P=0.009) and those with calcium levels ranging from 8 to 8.6mg/dL (P=0.001) had lower mean vitamin D levels compared to individuals with calcium levels≤8mg/dL. The details of patient characteristics are reported in Table 1.

Table 1. General and clinical characteristics based on serum calcium levels

Factors		Quartile of serum calcium (mg/dL)				
		Quartile 1 (≤ 8 mg/dL) N= 25, 31.25%	Quartile 1_3 (8 – 8.6 mg/dL) N = 37, 46.25%	Quartile 3 (≥ 8.6 mg/dL) N = 18, 22.50%	Total N = 80, 100%	P-value
General information						
Age (Years)		43.76±12.60	41.43±9.58	40.55±10.51	41.96±10.74	0.583
Gender	Female	13 (52.0)	12 (32.43)	5 (27.78)	30 (37.50)	0.185
	Male	12 (48.0)	25 (67.57)	13 (72.22)	50 (62.50)	
Current smoker (Yes)		6 (24.0)	9 (24.32)	3 (16.67)	18 (22.50)	0.797
Body Mass Index (BMI, Kg/m^2)		24.99±2.92	24.12±2.67	26.22±4.80	24.87±3.38	0.265
Hemodynamic assessment						
Systolic blood pressure (mmHg)		124.16±15.81	122.37±8.22	124.44±15.51	123.4±12.63	0.855
Diastolic blood pressure (mmHg)		83.56±10.33	81.54±9.26	79.61±6.77	81.73±9.13	0.375
Heart rate (pulse per minute)		85.72±18.37	82.05±9.85	88.33±17.59	84.61±14.83	0.441
Ejection Fraction (%EF)		50.32±4.47	50.0±5.40	51.39±4.47	50.41±4.90	0.634
Medical history (Yes)						
Diabetes		9 (36.0)	9 (24.32)	5 (27.78)	23 (28.75)	0.605
Hypertension		11 (44.0)	12 (32.43)	9 (50.0)	32 (40.0)	0.407
Dyslipidemia		2 (8.0)	3 (8.11)	3 (16.67)	8 (10.0)	0.626
Drug history (Yes)						
ACE I		2 (8.0)	8 (21.62)	4 (22.22)	14 (17.50)	0.332
ARB		11 (44.0)	13 (35.14)	9 (50.0)	33 (41.25)	0.544
Beta blocker		10 (40.0)	16 (43.24)	10 (55.56)	36 (45.0)	0.574
Diuretic		17 (68.0)	23 (62.16)	13 (72.22)	53 (66.25)	0.742
Nitrates		3 (12.0)	3 (8.11)	3 (16.67)	9 (11.25)	0.536
Statin		13 (52.0)	13 (35.14)	11 (61.11)	37 (46.25)	0.152
Antiplatelet		11 (44.0)	13 (35.14)	6 (33.33)	30 (37.50)	0.715
Laboratory results						
Serum creatinine (mg/dL)		3.96±1.003	4.12±1.25	4.51±1.10	4.16±1.15	0.308
Serum albumin (g/dL)		3.30±0.27	3.21±0.36	3.35±0.35	3.27±0.33	0.274
Serum phosphorus (mg/dL)		6.22±1.35	6.07±1.50	5.85±1.57	6.07±1.46	0.770
Serum calcium *phosphorus		47.98±10.97	51.26±12.70	52.61±14.42	50.54±12.58	0.446
Serum 25(OH)D (Vitamin D, ng/mL)		34.12±5.65	28.81±5.31**	28.77±6.15**	30.46 ± 6.07	<0.001*
Intact Parathyroid Hormone (iPTH, pg/mL)		534.36±136.53	477.89±178.10	483.39±173.37	496.77 ± 165.05	0.418

Data described as mean ± standard deviation or frequency and percentage

*Statistically significant, P-value<0.05

**Statistically significant based on post hoc analysis using Bonferroni correction

Table 2 shows the results of cardiopulmonary function and O_2 saturation categorized by serum calcium levels. The prevalence of inefficient ventilation based on VE/VCO_2 in patients with a serum calcium level ≥8.6 mg/dL was found to be 83.33%, while in those with serum calcium levels ranging from 8 to 8.6 mg/dL and ≤ 8 mg/dL, the prevalence was 62.16% and 60%, respectively. However, this difference was not statistically significant (P = 0.216). According to the results, no statistically significant differences were observed among any of the CPET parameters at different serum calcium levels (P > 0.05). Furthermore, after examining the correlation between CPET parameters and serum calcium, no statistically significant and meaningful correlations were found for any of the parameters with serum calcium (P > 0.05) (Table 2).

Table 3 shows the results of the univariate and multivariable analyses from the logistic regression model regarding the factors associated with increased ventilation demand during exercise based on VE/VCO_2. According to the results of the univariate analysis, the history of hypertension and a history of ARB medication use were significantly associated with increased ventilation demand during exercise.

Table 2. Cardiopulmonary function based on CPET parameters and oxygen utilization based on serum calcium levels and their correlation.

Factors	Quartile of serum calcium (mg/dL)					Correlation coefficient (rho)*	P-value
	Quartile 1 (≤ 8 mg/dL) N=25, 31.25%	Quartile 1 - 3 (8–8.6 mg/dL) N=37, 46.25%	Quartile 3 (≥ 8.6 mg/dL) N=18, 22.50%	Total N=80, 100%	P-value		
VO_2 (mL/kg/min)	19.39±3.05	18.60±2.69	18.52±3.54	18.83±2.99	0.530	-0.045	0.689
VE (L/min)	62.16±4.84	60.56±5.15	63.39±7.95	61.70±5.84	0.343	0.015	0.891
PET CO_2 (mmHg)	30.36±2.58	29.86± 2.68	28.89±2.37	29.8 ± 2.61	0.211	-0.149	0.186
Efficient ventilation (35 – 40 mmHg)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	N/A	-	-
inefficient ventilation (< 35mmHg)	25 (100)	37 (100)	18 (100)	80 (100)			
Peak VO_2 (mL/kg/min)	56.92±7.72	56.56±4.94	56.16±3.69	56.58±5.68	0.610	0.012	0.914
VE/VCO_2 (L/min)	35.96±2.16	36.36±2.14	37.12±3.18	36.41±2.42	0.131	0.171	0.128
Efficient ventilation (≤ 35 l/min)	10 (40.0)	14 (37.84)	3 (16.67)	27 (33.75)	0.216	-	-
Inefficient ventilation (> 35 l/min)	15 (60.0)	23 (62.16)	15 (83.33)	53 (66.25)			
O2 saturation (%)	94.96±3.78	96.27±1.53	96.22±1.80	95.85±2.54	0.253	0.136	0.228

N/A: Not Applicable

*Correlation coefficient of each factor with Serum calcium (mg/dL)

Table 3. Results of univariate and multivariable logistic regression about the association between clinical factors and increased ventilatory demands during exercise (VE/VCO_2 >35 l/min)

Factors	Univariate		Multivariable	
	Crude OR,95% CI	P-value	Adjusted OR,95%CI	P-value
Age (years)	0.98 (0.94 – 1.02)	0.453	0.98 (0.93 – 1.04)	0.723
Gender				
Female	Reference	0.302	Reference	0.185
Male	0.59 (0.22 – 1.59)		0.42 (0.12 – 1.50)	
Body Mass Index (BMI, Kg/m²)	0.95 (0.82 – 1.09)	0.473	0.84 (0.68 – 1.02)	0.086
History of hypertension				
No	**Reference**	**0.045***	Reference	0.882
Yes	**0.37 (0.14 – 0.98)**		0.83 (0.08 – 8.58)	
ARB				
No	**Reference**	**0.022***	Reference	0.291
Yes	**0.32 (0.12 – 0.84)**		0.30 (0.03 – 2.77)	
Beta blocker				
No	Reference	0.137	Reference	0.089
Yes	2.07 (0.79 – 5.44)		3.08 (0.84 – 11.26)	
Serum calcium (mg/dL)				
≤ 8 mg/dL (Quartile 1)	Reference	-	Reference	-
8 – 8.6 mg/dL (Quartile 1 – 3)	1.09 (0.38 – 3.09)	0.864	1.22 (0.34 – 4.36)	0.756
≥ 8.6 mg/dL (Quartile 3)	3.33 (0.76 – 14.57)	0.110	**6.93 (1.07 – 44.59)**	**0.041***
Serum calcium *phosphorus	0.96 (0.92 – 1.003)	0.074	0.95 (0.90 – 1.006)	0.083
Serum Albumin (g/dL)	3.85 (0.93 – 15.84)	0.061	5.05 (0.90 – 28.19)	0.065

OR, 95%CI: Odds Ratio, 95% Confidence Interval

Goodness of fit assessment of multivariable model: Area Under the Curve- Receiver Operating Characteristic (AUC-ROC)=80%

Hosmer-Lemeshow test, Chi-square (P-value)=8.38 (0.397)

After adjusting for the probable confounding variables in the final multivariable model, it was found that only serum calcium levels had a statistically significant association with increased ventilation demand during exercise (VE/VCO_2 >35 L/min**)** (P=0.041). Specifically, patients with serum calcium levels ≥ 8.6 mg/dL had approximately 7 times higher odds of increased ventilation demand (VE/VCO_2 >35 L/min**)** compared to those with calcium levels ≤ 8 mg/dL (OR=6.93, 95% CI=1.07-44.59, P=0.041) (Table 3).

DISCUSSION

In this comprehensive study, the researchers investigated a cohort of 80 patients with CKD stages 3 to 5 to explore various facets of cardiopulmonary function and their associations with biochemical markers. The cohort exhibited a gender imbalance, with a predominance of males, and an average age of 42 years. Assessing kidney function, the study examined serum creatinine levels and GFR, categorizing participants into different CKD stages. Cardiopulmonary function and oxygen utilization were extensively scrutinized, revealing insights into parameters such as VO_2, VE, PET CO_2, and VE/VCO_2, providing a comprehensive picture of the study participants' physiological responses during exercise. In subsequent analyses, the researchers explored potential associations between various variables and cardiopulmonary parameters. The study also aimed to establish cutoff values for identifying cardiopulmonary test disorders, with a particular focus on calcium and phosphorus levels. The findings underscore the multifaceted relationships between biochemical markers, cardiopulmonary function, and CKD and highlight the potential utility of calcium levels as a diagnostic marker for cardiopulmonary test disorders in this population.

A significant finding was the inverse relationship between serum calcium and vitamin D levels. Patients with serum calcium levels ≥ 8.6 mg/dL and those in the 8–8.6 mg/dL range had significantly lower vitamin D levels than those with calcium ≤ 8 mg/dL (P=0.001–0.009). This relationship aligns with physiological feedback mechanisms where elevated calcium suppresses parathyroid hormone, potentially reducing the conversion of vitamin D to its active form.

While the prevalence of ventilatory inefficiency (VE/VCO_2 > 35 L/min) was highest in patients with calcium≥8.6 mg/dL (83.33%), the difference across calcium quartiles was not statistically significant (P=0.216). However, multivariable logistic regression revealed that elevated serum calcium (≥ 8.6 mg/dL) independently increased the odds of inefficient ventilation (OR=6.93; 95% CI=1.07–44.59; P=0.041). This suggests a potential role of calcium dysregulation in exacerbating ventilatory demands during exercise.

In this article, we present the findings and discussion derived from a comprehensive study aimed at elucidating calcium and phosphorus disorders in chronic kidney failure patients exhibiting abnormalities in cardiopulmonary exercise tests. CKD represents a significant health concern, affecting a substantial portion of the population in the United States and worldwide. The management of CKD is complex, as it encompasses not only the renal system but also various cardiovascular and metabolic aspects that can impact patients' overall well-being.

Our study is situated within the context of existing literature, which has increasingly recognized the importance of assessing cardiopulmonary function in CKD patients. Previous research has explored the effects of exercise on cardiopulmonary function indices in CKD patients, with mixed results(12). While some studies have shown improvements in parameters like peak oxygen uptake (VO_2) with exercise interventions, the variability in findings highlights the need for further investigation in this area (12). Our study contributes to this discussion by focusing on CKD patients with cardiopulmonary exercise test abnormalities, shedding light on potential biochemical markers that may influence exercise tolerance and cardiopulmonary function.

One of the key findings in our study was the significant association between calcium levels and cardiopulmonary

test disorders. While the calcium-phosphorus product did not yield a suitable cutoff, calcium levels demonstrated diagnostic potential, with an AUC of 0.561. Notably, a calcium level of 8.65, with 28% sensitivity and 89% specificity, appeared as a promising cutoff for discerning cardiopulmonary test disorders. This finding aligns with the literature, as calcium has been previously implicated in cardiovascular and muscular function (13). Calcium plays a crucial role in cardiac muscle contraction and electrical conduction within the heart (14). Adequate calcium levels are necessary for the heart to pump blood effectively (15). In CKD patients, disturbances in calcium metabolism can lead to vascular calcification, a process where calcium deposits accumulate in blood vessels (16). This calcification can stiffen the arteries, increase blood pressure, and reduce the heart's ability to pump blood efficiently (17). These changes in cardiovascular function can manifest as exercise intolerance and abnormal cardiopulmonary test results. Calcium is also vital for the contraction of skeletal muscles (17). In CKD, muscle weakness and wasting are common due to factors such as metabolic acidosis, inflammation, and altered calcium levels. Lower calcium levels can lead to impaired muscle contraction and reduced exercise capacity. This muscular dysfunction can contribute to abnormal cardiopulmonary exercise test results (18).

Moreover, in CKD, the impaired filtration and excretion of phosphorus can result in elevated serum phosphorus levels. Elevated phosphorus levels can stimulate the release of parathyroid hormone (PTH), which, in turn, can disrupt calcium homeostasis (19). PTH can lead to increased calcium resorption from bones, potentially causing bone disease in CKD patients (20). These disturbances in calcium and PTH levels can affect muscle and cardiovascular function, contributing to exercise intolerance and abnormal test results (21).

In contrast, serum phosphorus levels did not appear to hold diagnostic value in the context of cardiopulmonary disorders, as indicated by an AUC of 0.370. These results are consistent with existing literature that has suggested associations between hyperphosphatemia and adverse cardiovascular outcomes in CKD patients (22). However, the lack of diagnostic significance for serum phosphorus in our study highlights the complex nature of CKD-related disorders and the need for more comprehensive assessments.

Our study contributes to the existing body of knowledge by shedding light on calcium and phosphorus disorders in CKD patients with cardiopulmonary exercise test abnormalities, an area with limited prior research. The identification of potential biomarkers, such as calcium, that may influence exercise tolerance and cardiopulmonary function opens avenues for future research and interventions aimed at enhancing adaptation and patient outcomes within this population.

There were no statistically significant differences in demographic, clinical, or cardiopulmonary parameters (e.g., VO_2, systolic blood pressure, or oxygen saturation) across calcium quartiles. Additionally, the correlation analysis did not reveal any meaningful relationships between serum calcium and cardiopulmonary exercise testing (CPET) parameters.

Univariate analysis indicated that a history of hypertension and angiotensin receptor blocker (ARB) use were significantly associated with increased ventilatory demands during exercise. However, these associations were not significant in the multivariable model. This attenuation might reflect confounding effects or the stronger influence of serum calcium levels in the adjusted model

The multivariable logistic regression model demonstrated good predictive performance with an AUC of 80% and acceptable calibration based on the Hosmer-Lemeshow test (P=0.397). This reinforces the robustness of the findings regarding serum calcium's association with ventilatory demands.

CONCLUSION

This study highlights the complex interplay between serum calcium levels, vitamin D, and ventilatory inefficiency in CKD patients. The significant association

between higher calcium levels and increased ventilatory demands during exercise underscores the need for careful calcium and vitamin D management in this population. Further research should explore mechanistic pathways and interventions to mitigate these effects.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of interest

There is no conflict of interest to declare.

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