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Evaluation of Serum Fibroblast Growth Factor 23 for Cardiovascular Risk Prediction in Chronic Kidney Disease Patients: A Study Using the SCORE2 Risk Model

E Vasudevan[1],B.Shanthi[2],Jainulavudeen Mohamed Rabeek[3],M. Vasanthan[4],Mary Chandrika Anton [5],S.Kalaiarasi[6],B.Krishnaprashanth[7]

[1] Tutor, Department of Biochemistry, Sree Balaji Medical College and Hospital, Chrompet, Chennai, Tamilnadu, India, Chennai – 600044. Orcid –0000-0002-8923-7199

[2]Professor, Department of Biochemistry, Sree Balaji Medical College and Hospital,Chrompet Chennai ,Tamil Nadu India, Chennai – 600044.Orcid – 0000-0002-7435-5985

[3]Senior resident, ESIC MEDICAL COLLEGE & PGIMSR, Ashok Pillar Main Rd, K. K. Nagar, Chennai, Tamil Nadu 600078

[4]Professor, Department of Biochemistry, Chettinad Health and Research Institute, Chettinad Academy of Research and Education, Kelambakkam-603103, Chengalpattu district, Tamil Nadu. ORCID ID: 0000-0002-3330-2027

[5]Associate Professor, Department of Biochemistry, Sree Balaji Medical College and Hospital,Chrompet,Chennai,Tamilnadu, India, Chennai – 600044.Orcid –0000-0003-4601-0792

[6]Lecturer,Mailam Nursing College Mailam Engineering College Campus Tindivanam, Taluk, Tindivanam, Mailam, Tamil Nadu 604304

[7]Assistant Professor, Department of Community Medicine, Sree Balaji Medical College and Hospital,Chrompet,Chennai,Tamilnadu, India, Chennai – 600044.

Abstract

Background: Cardiovascular disease (CVD) is a major public health problem and the leading cause of morbidity and mortality in patients with chronic renal disease (CKD). The utility of Serum Fibroblast Growth Factor 23 (FGF23) as predictor of cardiovascular risk among CKD patients is evaluated in this study using SCORE2 risk model.

Methods: To categorize participants into low medium and high cardiovascular risk groups, the SCORE2 risk model was used in this cross-sectional study of 150 CKD patients aged 40–75 years. Regression and ROC analysis of serum FGF23 levels and key cardiovascular biomarkers were performed.

Results: We found that higher FGF23 levels were associated with higher cardiovascular risk (low risk: 64.88 pg/ml vs. High risk: 650.75 pg/ml; $p<0.001$). Through regression analysis, we demonstrated strong associations between FGF23 and inflammatory markers (hscrp, $R^2=0.777$) as well as oxidative stress markers (MDA, $R^2=0.738$). Analysis by ROC revealed high predictive capacity of FGF23 (AUC=0.851).

Conclusion: FGF23 may serve as a biomarker for early cardiovascular risk stratification in CKD and a good marker for inclusion in cardiovascular risk models.

Keywords: Chronic Kidney Disease, Cardiovascular Risk, Fibroblast Growth Factor 23, SCORE2 Risk Model, Oxidative Stress.

INTRODUCTION:

Chronic kidney disease (CKD) has become a considerable global public health problem, representing approximately 10% of the total population and its co radicating factors are responsible for more morbidity and mortality[1] . Cardiovascular disease (CVD) is one of the most important complications of CKD, and the leading cause of death in this patient population[2]. Cardiovascular risk in CKD patients is multifactorial, and includes both traditional risk factors, such as hypertension and dyslipidemia, and other nontraditional factors like uremic toxins, oxidative stress and disturbances of mineral metabolism[3]. Kidney dysfunction, on the other hand, has a profound impact in cardiovascular health and therefore needs to identify biomarkers that give insight into early cardiovascular risk stratification and therapeutic intervention [4].Fibroblast growth factor 23 (FGF23) is a novel biomarker at the intersection of mineral metabolism and cardiovascular pathology [5], and is a hormone that is primarily secreted by the osteocyte. Originally defined by its function in phosphate homeostasis and vitamin D metabolism, FGF23 levels

rise early in CKD in an adaptive attempt to compensate for phosphate imbalance[6]. In addition, increased FGF23 was associated with poor cardiovascular outcomes, including left ventricular hypertrophy (LVH), vascular calcification, and arterial stiffness. These effects are independent of classical risk factors suggesting a potential role as a novel biomarker of the cardiovascular risk in CKD patients [7,8] . The complex and multifaceted pathophysiological mechanisms linking FGF23 to cardiovascular disease are detailed [9]. Interestingly, FGF23 induces LVH by activating FGFR4 signaling pathway causing myocardial fibrosis and hypertrophy. Under the high FGF23 concentration, this activation can occur independently with the co-receptor α-klotho [10]. High FGF23 elevations are also linked to endothelial dysfunction, systemic inflammation, which are both independently associated with the progression of vascular calcification and atherosclerosis [11]. These results suggest that FGF23 may be an integrative biomarker related to renal and cardiovascular function.

However, clinical utility of FGF23 to stratify risk of cardiovascular outcomes in CKD is still underexplored despite growing evidence linking FGF23 to cardiovascular outcomes in CKD. Serum FGF23 levels and their associations with key cardiovascular biomarkers such as its markers of inflammation and oxidative stress may hold the key to understanding its prognostic value. Combining FGF23 into existing cardiovascular risk prediction models, such as SCORE2 framework, increases the sensitivity and specificity and thereby contribute to the earlier identification of high risk individuals. Therefore, this study sought to examine the value of serum FGF23 as a cardiovascular risk stratification biomarker for CKD. This research aims to fill these gaps in the risk assessment tools by analyzing FGF23 levels and how they are associated with cardiovascular markers, thereby contributing to a early detection strategy for cardiovascular risk, sensitive and reliable, in this high risk population.

MATERIALS AND METHODS

Study Design

This cross-sectional study was conducted at a tertiary care centre South India on 150 participants, after obtaining intuitional ethical clearance . Adult CKD patients aged 40–75 years attending Nephrology OP were the study population. Participants were stratified into three groups based on SCORE2 risk categories: Participants are divided into low risk (<5%), moderate risk (5–10%) and high risk (>10%) [12]. Supplementary Figure 1 contained detailed participant selection.

All CKD patients with a known case who had not had any acute complications within the last three months were inclusion criteria. We excluded patients with recent cardiovascular events (less than 6 months prior), end stage kidney disease, severe systemic illnesses, malignancy, autoimmune diseases, lactating or pregnant women. The SCORE2 model for cardiovascular risk assessment was used including age, gender, smoking status, systolic blood pressure and total cholesterol to estimate 10-year cardiovascular mortality risk.

Biochemical analysis

Renal function, cardiovascular risk, and oxidative stress were evaluated by biochemical parameters. Venous blood was taken from participants via standard phlebotomy techniques using venous blood samples. 5 ml of blood was collected in a red top vacutainer tube for serum analysis; and 2 ml of blood was collected in an EDTA tube for HbA1c analysis. Red top tube was centrifuged at 4000 rpm for 15 mins and serum was separated. Serum urea, creatinine, fasting plasma glucose, lipid profile was estimated immediately on a Biosystem BA400 analyzer whereas glycated hemoglobin (HbA1c) estimated on a Biorad D10 analyzer. The estimated glomerular filtration rate (eGFR) was calculated by formula to assess renal function and spot urine samples were collected to obtain urinary albumin to creatinine ratio.

$eGFR = 175 \times \text{Serum } Cr^{-1.154} \times age^{-0.203} \times 1.212$ (if patient is black*) $\times$ 0.742 (if female) [13.]

The 10-year cardiovascular risk was evaluated using the SCORE2 (Systematic Coronary Risk Evaluation version 2) framework evaluated with the ESC CVD Risk Calculation [12] based on age, sex, systolic blood pressure, total cholesterol, HDL cholesterol and smoking status. Remaining serum was aliquoted and stored at – 20°C until further testing for biomarkers. Fibroblast Growth Factor 23 Serum levels were measured with an Elabscience ELISA kit with a sensitivity of 9.38 pg/ml and a detection range of 15.63–1000 pg/ml. High sensitivity C-reactive protein (hsCRP) was determined using an Eagle Biosciences ELISA kit with 0.10 mg/L sensitivity and 0.1 - 50 mg/L detection range. Measurements of

malondialdehyde (MDA), a marker of lipid peroxidation, and total antioxidant capacity (TAC), as an indicator of the body's overall antioxidant defence capacity, were used as markers of oxidative stress. Total antioxidant capacity was measured by Elabscience ELISA kit with sensitivity 0.049 mmol/L, and the detection range of the ELISA kit was 0.049–2.5 mmol/L; malondialdehyde was measured by Elabscience ELISA kit with sensitivity of 18.75 ng/mL and detection range of 31.25–2000 ng/mL.

Statistical Analysis

All statistical analyses were conducted using SPSS (Statistical Package for the Social Sciences, version 25). The normality of the data was assessed using the Shapiro-Wilk test, confirming that the data were normally distributed. As the data met the assumptions for parametric testing, continuous variables were presented as mean ± standard deviation (SD), and group comparisons were performed using one-way ANOVA. Categorical variable was compared using Chi-Square test,

Linear Regression was applied to investigate the relationship between FGF23 and renal and cardiovascular markers. Diagnostic sensitivity and specificity of serum FGF23 in differentiating groups of varying cardiovascular risk levels was evaluated using Receiver Operating Characteristic curve analysis. Furthermore, mediation analysis was performed to determine the independent relationships of serum FGF23 levels with cardiovascular risk. All tests were statistical significance defined by a $p < 0.05$.

Results:

Table 1: Comparative analysis of demographic, biochemical, and clinical parameters across patient groups based on SCORE-2.

Parameters	Group A(<5%) (n=52)	Group B (5–10%) (n=53)	Group C (>10%) (n=45)	*p* value
Age	41.37 ± 7.74	42.03 ± 6.85	44.41 ± 6.79	0.241
Male, n(%)	22 (43)	26 (49)	26 (58)	0.674
Female, n(%)	30 (57)	27 (51)	19 (42)	0.056
FBS (mg/dL)	92.03 ± 6.68	152.65 ± 51.4	183.93 ±71.67	0.021*
PPBS (mg/dL)	99. 93 ± 24.97	222.58 ± 87.26	275.31 ± 72.57	0.037*
HbA1c (%)	5.24 ± 0.13	6.04 ± 0.28	7.2 ± 0.35	<0.001**
SBP	120.94 ± 5.79	140.34 ± 5.56	146.59 ± 11.22	<0.001**
DBP	75.32 ± 2.73	85.41 ± 2.94	87.72 ± 5.32	<0.001**
T. Cholesterol (mg/dL)	159.62 ± 47.12	201.5 ± 47.39	206.62 ± 47.70	<0.001**
TGL (mg/dL)	103.82 ± 47.38	151.68 ± 68	158. 62 ± 97.12	0.011*
LDL-c (mg/dL)	144.72 ± 47.04	143.27 ± 38.47	140.6 ± 23.04	0.722
VLDL-c (mg/dL)	21.82 ± 8.85	30.18 ± 13.65	37.17 ± 12.44	0.112
HDL-c (mg/dL)	51.98 ± 9.18	47.93 ± 10.7	39.75 ± 10.5	<0.001**
Creatinine (mg/dL)	0.75 ± 0.15	0.71 ± 0.155	2.76 ± 1.08	<0.001**
Urea (mg/dL)	18.93 ± 4.71	19.4 ± 4.66	42.79 ± 13.03	<0.001**
eGFR	106.35 ± 23.31	105.62 ± 24.45	50.52 ± 18.78	<0.001**
UACR	16.30 ± 6.9	53.39 ± 10.40	185.01 ± 67.2	<0.001**
Diabetes, n(%)	7 (13)	25 (47)	20 (44)	0.023*
Smoking, n(%)	11 (21)	18 (34)	16 (36)	0.735
Alcohol, n(%)	9 (17)	11 (21)	6 (13)	0.580

*The table displays means ± SD for continuous variables and counts (percentages) for categorical variables. ANOVA and Chi-square tests were used for continuous and categorical variables, respectively. Asterisks indicate significance levels: * ($p < 0.05$) and ** ($p < 0.01$)*

A significant difference can be observed across key metabolic and renal parameters when compared by patient groups of different cardiovascular risk. In Group C fasting blood sugar (p=0.021), postprandial blood sugar (p=0.037) and HbA1c (p<0.001) are significantly higher than in Group A and B. Moreover, this group also has the highest blood pressure (mean SBP: 146.59 mmHg, mean DBP: 87.72 mmHg, both p<0.001). Group C experiences substantial impairment in renal function with mean creatinine of 2.76

mg/dL, mean urea of 42.79 mg/dL and significant decrease in estimated glomerular filtration rate (eGFR) of 50.52 (p<0.001). Accordingly, total cholesterol is 206.62 mg/dL, triglycerides 158.62 mg/dL (both p<0.001) and HDL cholesterol is significantly lower at 39.75 mg/dL (p<0.001) [Table 1].

Table 2: Comparative assessment of inflammatory, oxidative stress, and renal marker across patient groups based on SCORE-2.

Parameters	Group A(<5%) (n=52)	Group B (5–10%) (n=53)	Group C (>10%) (n=45)	*p* value
hsCRP (mg/L)	1.5 ± 0.95	6.07 ± 2.1	15.63 ± 4.21	<0.001**
MDA (ng/ml)	67.11 ± 25.06	131.53 ± 14.28	219.67 ± 34.50	<0.001**
TAC (umlo/L)	1.80 ± 0.37	1.12 ± 0.22	0.54 ± 0.18	<0.001**
FGF23 (pg/mL)	64.88 ± 18.08	219.66 ± 58.10	650.75 ± 171.85	<0.001**

*The table presents data as mean ± standard deviation for biomarkers hsCRP, MDA, TAC, and FGF23 across three patient groups. ANOVA was used to analyze differences. Asterisks indicate significance levels: * (p < 0.05) and ** (p < 0.01)*

Table 2 reveals that High-sensitivity C-reactive protein levels show a clear trend with increasing values across the groups (p<0.001). Additionally, Malondialdehyde (MDA), a lipid peroxidation marker, elevated Group C (p <0.001). A corresponding decline is also observed for total antioxidant capacity in Group C (p<0.001). FGF23 levels also markedly increase across the groups, from 64.88 pg/mL in Group A, 219.66 in Group B, and 650.75 in Group C (p<0.001). These results indicate a strong link between cardiovascular risk and elevated concentrations of inflammatory and oxidative stress markers.

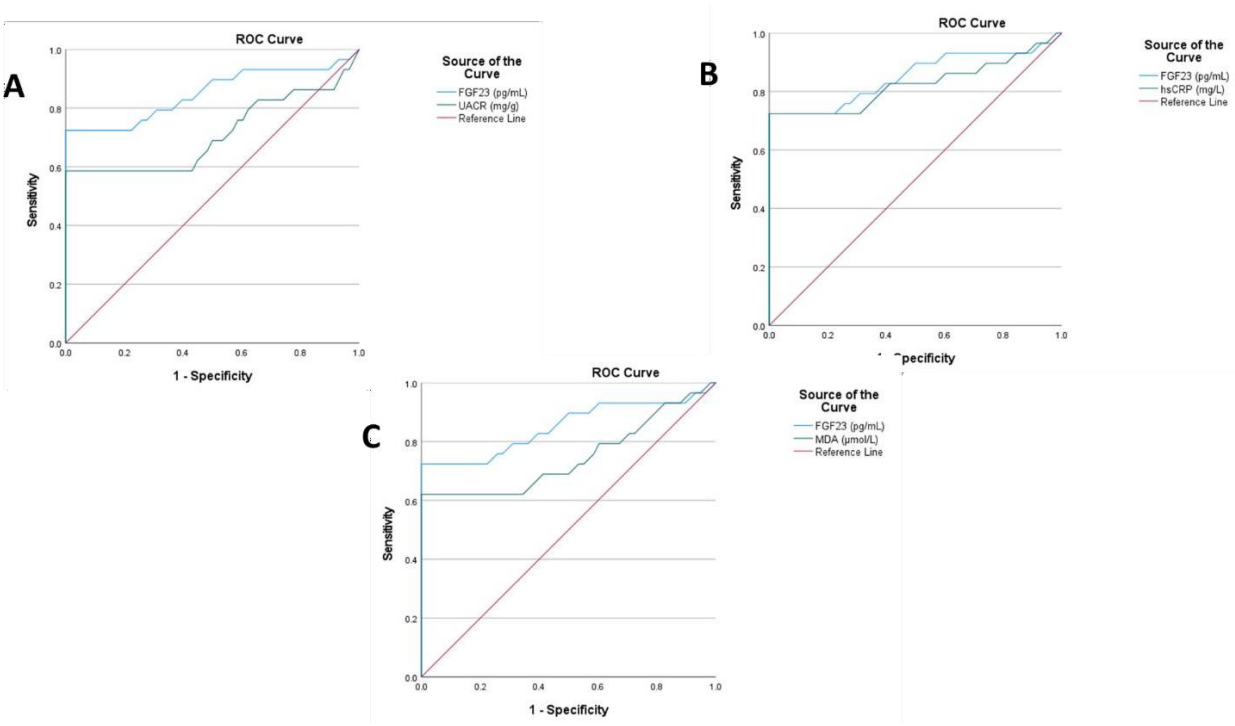
Table 3: Regression analysis between FGF23 levles and key renal, inflammatory, oxidative stress biomarkers

Parameter	R Square	F-Statistic	*p*-value	Coefficient (b1)
eGFR	0.468	74.887	<0.001**	-4.992
UACR (mg/g)	0.707	204.834	<0.001**	2.748
hsCRP (mg/L)	0.777	295.570	0.031*	26.944
MDA (µmol/L)	0.738	238.884	0.043*	92.098
TAC (mmol/L)	0.606	130.919	0.013*	-359.518
Creatinine	0.400	56.623	<0.001**	213.445
Urea	0.434	65.046	<0.001**	9.817

*Linear regression analyses assessing the association between FGF23 levels and various biochemical markers. Asterisks indicate significance levels: * (p < 0.05) and ** (p < 0.01)*

Regression analyses show significant relationships between FGF23 concentrations and independent biochemical and physiological markers. hsCRP appeared with the highest R2 (77.7%) and is a strong predictor for FGF23. UACR and MDA also had strong associations to FGF23, with R2 of 70.7% and 73.8%, respectively, indicating their substantial impact on FGF23. Other traditional, renal function markers like eGFR and urea were also significant predictors but explained a lower FGF23 variance: R2 = 46.8% and R2 = 43.4%, respectively [Table 3] [Supplementary Figure 2].

Figure 1: Comparative ROC Analysis of FGF23, UACR, hsCRP, and MDA as Predictors of Cardiovascular risk in CKD patients



This figure shows, A. ROC comparison between UACR and FGF23, B. ROC comparison between hsCRP and FGF23, C. ROC comparison between MDA and FGF23

The ROC analysis showed robust predictive capability of FGF23 alone, (AUC = 0.851, p < 0.001) or in combination with hsCRP (AUC = 0.825, p < 0.001) to determine cardiovascular risk in CKD patients. The optimal cutoff values of biomarkers FGF23, MDA, hsCRP, and UACR that best balance sensitivity and specificity. The cutoff threshold of FGF23 is set at 142.3173 pg/mL, with sensitivity and specificity of 72.4 and 84.5 percent, respectively. MDA marker at a cutoff of 4.0551 µmol/L was found to have a sensitivity of 62.1%, a specificity of 67.2%. We observed a higher sensitivity of 86.2% and specificity of 39.7% for hsCRP with a cutoff point of 1.7500 mg/L. UACR cutoff at 50.5934 mg/g, yielded a sensitivity of 58.6% and a specificity of 69%. These results highlight that both FGF23 and hsCRP are potentially useful biomarkers for early detection of increased cardiovascular risk in CKD patients [Figure 1].

Table 4: Mediation analysis of hsCRP on FGF23 Levels and Cardiovascular Risk in CKD Patients

Outcome	Predictor(s)	Coefficient	Standard Error	95% CI	*p*-value
hsCRP	FGF23	0.0103	0.0033	[0.0036, 0.0169]	0.0029*
SCORE-2	FGF23	0.0016	0.0002	[0.0012, 0.0020]	<0.0001**
SCORE-2	hsCRP	0.0480	0.0064	[0.0353, 0.0606]	<0.0001**
Direct Effect	FGF23 + SCORE-2	0.0016	0.0002	[0.0012, 0.0020]	<0.0001**

*Mediation analysis using the PROCESS macro by Andrew Hayes. Asterisks indicate significance levels: * (p < 0.05) and ** (p < 0.001)*

Our study documented significant relationships as are shown in Table 4. FGF23 plays a significant role in the predicting linearity of hsCRP, that is, FGF23 and hsCRP increase concurrently as FGF23 increases

(coefficient = 0.0103, p = 0.0029). We further characterize this relationship and its potential on cardiovascular risk prediction in CKD patients, FGF23 independently predicts risk (coefficient = 0.0016, $p < 0.0001$), suggesting that FGF23 is an independent direct risk factor. Moreover, hsCRP is a major mediator, and increases in hsCRP are highly associated with higher cardiovascular risk scores (coefficient = 0.0480, $p < 0.0001$). We found that FGF23 has a statistically significant indirect effect on grp through hsCRP. These results provide evidence that hsCRP is a mediator in the integration of FGF23 into cardiovascular risk.

DISCUSSION

It is well known that chronic kidney disease is part of an important global health issue with an estimated 700 million cases globally with huge impact on the patients and health care systems [14]. The CKD and cardiovascular disease intersection is a particularly severe burden owing to the fact that cardiovascular complications are the leading cause of death in persons with CKD [15]. Given its ability to track the disease, this presents an urgent need for additional predictive tools and biomarkers for improved early diagnosis and intervention, which might transform patient care globally [16].

Biomarker research holds great promise, and recently Fibroblast Growth Factor 23 has been identified as a regulator of mineral metabolism and a key marker for cardiovascular health in chronic kidney disease [17]. FGF23 promotes cardiovascular pathology through multiple mechanisms, including FGFR4-mediated myocardial hypertrophy, inflammation via the NF-κB signaling pathway, and oxidative stress induction [18]. The observed correlation with MDA and hsCRP in our study aligns with these mechanisms. That foundation is furthered by our research, which provides new data to harmonize FGF23 into current cardiovascular risk assessments. This could facilitate more precise and earlier prediction of cardiovascular events, and a clearer pathway to the use of targeted interventions to delay or prevent cardiovascular disease in patients with CKD.In our research, FGF23 adoption into the SCORE2 risk assessment framework has proven to increase its predictive capability suggesting that this biomarker can help to substantially improve cardiovascular risk stratification in CKD patients. This finding is consistent with a recent study by Kallmeyer et al, who also found that in FGF23 is a strong independent predictor of heart failure, and that higher levels of FGF23 are associated with a worse cardiovascular outcome, independently of other known risk factors and of mineral metabolism components [19]. Our study's mediation analysis augments this complexity by demonstrating that elevated FGF23 levels mediate the link between FGF23 and systemic inflammation, as represented by increased high sensitivity C-reactive Protein (hsCRP). This association leads to the inflammatory pathways being pivotal mediators of cardiovascular risk in this cohort and lends support to recent findings by Panwar et al, that elevated levels of hsCRP, together with FGF-23, predict adverse outcomes in CKD (including cardiovascular events), even after adjustment for classical renal risk factors [20]. Vasilkova et al in 2020 also studied that Monitoring both FGF-23 and hsCRP could improve risk stratification and management approaches in CKD patients, especially patients with diabetes [21].

While our findings revealed that oxidative stress markers with malondialdehyde and total antioxidant capacity are correlated to FGF23 levels which strongly support the role of FGF23 in cardiovascular risk prediction. Yet, Donovan et al. reported a lack of causal association in a Mendelian randomization study [22]. This discrepancy underscores the need for longitudinal studies to better delineate causation from correlation.However, our findings are promising, but our study is cross sectional, so we are unable to infer causal relationships. Longitudinal research is needed to clarify the temporal dynamics of FGF23 longitudinal levels and cardiovascular outcomes. These findings, although derived from a South Indian cohort, are potentially applicable to other populations. However, differences in CKD etiology and genetic factors necessitate validation in multi-ethnic cohorts. Overall, our study confirms that FGF23 is a potent cardiovascular predictor in the CKD population, and shifts the paradigm that can and should be used to assess and treat cardiovascular risks in CKD patients. Integrating FGF23 into standard risk models may allow clinicians to more accurately predict and intervene upon cardiovascular complications and provide a more tailored and effective approach to managing the dual burden of cardiovascular disease in the setting of CKD on a global scale.

CONCLUSION AND FUTURE DIRECTIONS:

This study confirms the utility of Fibroblast Growth Factor 23 as a useful cardiovascular risk biomarker in chronic kidney disease patients. According to the results, incorporation of FGF23 into the SCORE2 risk model to predict cardiovascular risk has improved predictions, suggesting that FGF23 could be useful for developing early intervention strategies. There is a strong correlation of elevated FGF23 with inflammation and oxidative stress, and these appear promising pathways for therapeutic strategies. To validate the predictive value of FGF23 in this regard is, however, necessary in longitudinal studies, as well as across diverse populations. Interventions targeting the inflammatory and oxidative pathways modulated by FGF23 should be tested using clinical trials to reduce cardiovascular complications and improve patient outcome in CKD. Such newly discovered inputs may additionally fuel further investigation into the molecular mechanisms tying FGF23 and cardiovascular pathology together, highlighting new therapeutic interventions which could fundamentally change the current strategy in managing cardiovascular disease in CKD patients.

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee at Sree Balaji Medical College and Hospital Ref no:002/SBMC/IHEC/2024/1653 and waived informed consent as the study population

Authors' contribution

Mr. E.Vasudevan conducted this research under the supervision of Dr. B. Shanthi. The discussion was written by, Jainulavudeen Mohamed Rabeek,M. Vasanthan,S.Kalaiarasi,Mary Chandrika anton

Availability of data and materials

All data generated and analyzed during this study are available upon request, and included in this published article. Data sharing is dependent upon permission from the health service and ethics approval.

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Conflict of interest

No potential conflicts of interest are reported.

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