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Clinical Significance of Kallikrein As A Diagnostic and Prognostic Biomarker in Cardiorenal Syndrome Associated with Chronic Heart Failure

Abdigaffar Gadaev
Professor, Department of Internal Medicine in Family Medicine No. 2, Tashkent State Medical University, Tashkent, 100190, Uzbekistan

Matluba Rakhimova
Associate Professor, Department of Internal Medicine, Alfraganus University, Tashkent, Tashkent, 100190, Uzbekistan

Jahongir Muzaffarov
Assistant, Department of Internal Medicine, Alfraganus University, Tashkent, 100190, Uzbekistan

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Abstract

Background. Chronic heart failure (CHF) remains one of the leading challenges in modern healthcare systems worldwide and is frequently accompanied by impaired renal function. The progressive and interrelated deterioration of cardiac and renal function leads to the development of cardiorenal syndrome (CRS), which significantly worsens patient prognosis. In recent years, alongside neurohumoral mechanisms, the kallikrein-kinin system has been increasingly recognized as an important contributor to CRS pathogenesis; however, its diagnostic value has not yet been sufficiently elucidated. Objective. To evaluate the diagnostic and potential prognostic significance of kallikrein levels in the early stages of cardiorenal syndrome developing in patients with chronic heart failure, and to determine their relationship with NT-proBNP, aldosterone, and renal function parameters. Methods. This prospective observational study included 115 patients with chronic heart failure classified as New York Heart Association (NYHA) functional classes II-III. Patients were divided into two groups according to functional class. Serum levels of kallikrein, NT-proBNP, aldosterone, cystatin C, and creatinine were measured. Glomerular filtration rate (GFR) was calculated using the CKD-EPI equation. Statistical analysis was performed using Student's t-test and Pearson correlation analysis. Results. Kallikrein levels were significantly lower in patients with NYHA class III compared to class II (535.86±12.37 vs. 778.79±17.8 ng/mL; p<0.001). In contrast, NT-proBNP levels were significantly higher (738.6±45.8 vs. 587.3±59.9 pg/mL; p<0.05). Kallikrein demonstrated a negative correlation with NT-proBNP (r = -0.51; p<0.001) and aldosterone (r = -0.48; p<0.001), while showing a positive correlation with GFR calculated based on cystatin C (r = 0.66; p<0.001). Conclusion. Decreased kallikrein levels are associated with increased severity of cardiorenal syndrome and exhibit inverse relationships with NT-proBNP and aldosterone, while correlating positively with renal function parameters. The combined assessment of these biomarkers may have potential clinical value for the early diagnosis and prognostic stratification of cardiorenal syndrome.

Keywords: Cardiorenal syndrome, kallikrein, NT-proBNP, cystatin C, aldosterone, chronic heart failure, biomarkers.

Introduction

Chronic heart failure (CHF) represents one of the most pressing challenges in contemporary cardiology, characterized by high morbidity and mortality rates [1,2]. Epidemiological data indicate that CHF affects millions of individuals worldwide, with a steadily increasing prevalence, particularly among the aging population [3,4]. As a terminal stage of various cardiovascular diseases, CHF is associated with a marked decline in quality of life and an unfavorable clinical prognosis [2,5].

In recent years, a high prevalence of comorbid conditions—particularly renal dysfunction—has been observed in patients with CHF [6,7]. According to multiple

studies, more than 50% of patients with CHF exhibit impaired renal function, which significantly contributes to disease progression and increases the risk of mortality [7,8]. The bidirectional and interdependent deterioration of cardiac and renal function has led to the clinical concept of cardiorenal syndrome (CRS) [9].

Cardiorenal syndrome is characterized by complex pathophysiological mechanisms involving hemodynamic alterations, activation of neurohumoral systems, inflammation, and oxidative stress [10–12]. In particular, the renin–angiotensin–aldosterone system (RAAS), the sympathetic nervous system, and natriuretic peptide pathways are considered key contributors to the pathogenesis of CRS [13,14].

More recently, the kallikrein–kinin system (KKS) has also emerged as an important regulatory pathway in cardiovascular and renal physiology [15]. This system exerts protective effects through vasodilation, enhancement of natriuresis, improvement of endothelial function, and anti-inflammatory actions [16]. However, several studies have reported a decline in kallikrein system activity with increasing severity of heart failure [17,18].

Despite growing interest in this pathway, the diagnostic and particularly prognostic significance of kallikrein in cardiorenal syndrome remains insufficiently investigated. In particular, comprehensive evaluations of its relationship with established biomarkers such as NT-proBNP, aldosterone, and indicators of renal function are still limited [19,20]. These gaps highlight the need for further in-depth investigation of the kallikrein system in this context.

Therefore, the aim of the present study was to assess the diagnostic and potential prognostic significance of kallikrein levels in the early stages of cardiorenal syndrome developing in patients with chronic heart failure, as well as to determine their relationship with key neurohumoral and renal function markers. It should be noted that the prognostic value of kallikrein in this study was considered exploratory, as it was not evaluated through long-term follow-up.

Methods

This study was conducted between 2024 and 2025 as a prospective, observational, single-center clinical investigation at the clinic of Tashkent State Medical University and a Republican Specialized Medical Center. The study protocol was approved by the local ethics committee, and written informed consent was obtained from all participants. The study was carried out in full accordance with the principles of the Declaration of Helsinki.

A total of 115 patients with chronic heart failure (CHF) secondary to ischemic heart disease or arterial hypertension were enrolled. The mean age of the participants was 66.2±1.3 years. The gender distribution was analyzed separately within each clinical group.

Patients were stratified into two groups according to the severity of heart failure based on the New York Heart Association (NYHA) classification: Group I included 30 patients with NYHA class II CHF, while Group II consisted of 85 patients with NYHA class III CHF.

Inclusion criteria comprised age over 40 years, presence of CHF corresponding to NYHA functional classes II–III, underlying ischemic heart disease or hypertension, and early-stage chronic kidney disease (CKD stages I–II). Exclusion criteria included acute heart failure, end-stage renal disease, severe hepatic insufficiency, acute inflammatory conditions, and active oncological diseases.

Venous blood samples were collected from all participants to determine serum levels of kallikrein, NT-proBNP, aldosterone, creatinine, and cystatin C, enabling a comprehensive assessment of both neurohumoral activity and renal function. Glomerular filtration rate (GFR) was calculated using the CKD-EPI equation based on creatinine and cystatin C levels.

In addition, all patients underwent instrumental examinations, including electrocardiography and echocardiography, to evaluate cardiac structure and function.

The study was carried out in several sequential stages. Initially, baseline clinical, laboratory, and instrumental parameters were assessed in all patients. Subsequently, intergroup comparisons were performed, followed by correlation analysis to evaluate the relationships between the studied biomarkers.

Statistical analysis was performed using Microsoft Excel (2021). Data were expressed as mean ± standard error of the mean (M±m). Differences between groups were assessed using Student’s t-test. Correlations between variables were determined using Pearson’s correlation coefficient. A normal distribution of data was assumed. A p-value of <0.05 was considered statistically significant.

The study design was exploratory in nature, with a primary focus on identifying correlations between biomarkers. The sample size was determined based on the available patient population in the clinical setting and was considered sufficient to detect statistically significant differences between groups.

Results

A total of 115 patients were included in the study, and their clinical, laboratory, and instrumental parameters were systematically analyzed according to NYHA functional class. The findings revealed that worsening heart failure was associated with significant alterations in both renal function and neurohumoral activity.

Assessment of renal function demonstrated that the glomerular filtration rate (GFR) calculated based on creatinine was 88.4±1.57 mL/min/1.73 m² in patients with NYHA class II, whereas it decreased to 79.3±1.67 mL/min/1.73 m² in those with NYHA class III, with the difference being statistically significant ($p<0.001$). A similar trend was observed for cystatin C–based GFR, which was 61.3±3.6 mL/min/1.73 m² in class II and declined to 53.5±1.06 mL/min/1.73 m² in class III

($p<0.05$). Notably, lower GFR values derived from cystatin C compared to creatinine suggest a higher sensitivity of cystatin C in detecting early renal dysfunction.

In contrast, neurohumoral and biochemical markers exhibited opposite patterns. Serum kallikrein levels were significantly reduced in patients with NYHA class III compared to class II (535.86±12.37 vs. 778.79±17.8 ng/mL), representing a 31.2% decrease ($p<0.001$). Conversely, NT-proBNP levels increased with disease severity, rising from 587.3±59.9 pg/mL in class II to 738.6±45.8 pg/mL in class III ($p<0.05$). Similarly, aldosterone levels showed a parallel increase, reaching 231±25.97 pg/mL and 293.9±18.09 pg/mL in classes II and III, respectively ($p<0.05$), indicating progressive activation of the renin–angiotensin–aldosterone system.

These findings confirm that increasing severity of heart failure is associated with deterioration of renal function, suppression of the kallikrein system, and activation of neurohumoral stress markers.

Correlation analysis further demonstrated significant relationships among the studied parameters. A negative correlation was observed between kallikrein and NT-proBNP, with coefficients of $r = -0.37$ ($p<0.05$) in NYHA class II and $r = -0.51$ ($p<0.001$) in class III, indicating that lower kallikrein levels are associated with greater severity of heart failure. Similarly, kallikrein showed an inverse relationship with aldosterone ($r = -0.36$ and $r = -0.48$, respectively), suggesting suppression of the kallikrein system in the context of RAAS activation.

Analysis of renal function revealed a positive correlation between kallikrein and cystatin C–based GFR ($r = 0.32$; $p<0.05$ in class II and $r = 0.66$; $p<0.001$ in class III), indicating that higher kallikrein levels are associated with better preserved renal function.

In addition, significant associations were identified with hemodynamic parameters. Kallikrein levels demonstrated a moderate positive correlation with left ventricular ejection fraction (LVEF), with $r = 0.55$ in NYHA class II and $r = 0.63$ in class III ($p<0.001$), suggesting a relationship between higher kallikrein levels and improved systolic function. Furthermore, a positive correlation was observed between kallikrein and the E/A ratio ($r = 0.61$ and $r = 0.70$; $p<0.001$), reflecting an association with diastolic function.

Overall, these results indicate that kallikrein is closely linked with cardiac function, renal function, and neurohumoral activation, supporting its potential role as an integrated biomarker in cardiorenal syndrome.

Discussion

The findings of the present study demonstrate that kallikrein levels have significant diagnostic and potential prognostic value in patients with cardiorenal syndrome developing in the context of chronic heart failure. A progressive decline in kallikrein levels was observed with increasing disease severity, suggesting attenuation of the protective mechanisms mediated by the kallikrein–kinin system. These observations are consistent with contemporary evidence indicating an imbalance between vasoregulatory systems in advanced heart failure [12,14,15].

A key strength of this study is the comprehensive evaluation of the relationship between kallikrein and both neurohumoral markers and renal function parameters in the early stages of cardiorenal syndrome. To our knowledge, such an integrated assessment has not been systematically addressed in previous studies. The results highlight the pivotal role of the kallikrein–kinin system in the complex pathophysiological interplay between cardiac and renal dysfunction.

The kallikrein–kinin system exerts important cardioprotective and renoprotective effects, including vasodilation, enhancement of endothelial function, promotion of natriuresis, and anti-inflammatory actions [15,16]. Therefore, reduced activity of this system may contribute to the progression of both cardiac and renal dysfunction. Previous studies have also reported an association between decreased kallikrein activity and worse clinical outcomes in heart failure [17,18], which is in agreement with our findings.

The observed inverse correlation between kallikrein and NT-proBNP ($r = -0.37$ to -0.51) reflects the complex interaction between neurohumoral pathways. NT-proBNP is a well-established biomarker of cardiac stress and is widely used to assess the severity of heart failure [10,16]. The concomitant increase in NT-proBNP and decrease in kallikrein levels may indicate the breakdown of compensatory mechanisms and progression toward a more decompensated state.

In addition, the negative association between kallikrein and aldosterone suggests an antagonistic relationship between the kallikrein–kinin system and the renin–angiotensin–aldosterone system. Elevated aldosterone levels are known to promote sodium and water retention, thereby increasing cardiac workload and contributing to disease progression [11,17]. The suppression of kallikrein in this context may further exacerbate these pathological processes.

Renal function analysis also yielded clinically relevant findings. The lower GFR values calculated using cystatin C compared to creatinine reinforce the higher sensitivity of cystatin C for early detection of renal impairment [6,18]. The positive correlation between kallikrein and GFR ($r = 0.32–0.66$) suggests that reduced kallikrein activity is associated with worsening renal function, further supporting its role as a potential biomarker in cardiorenal interactions.

Furthermore, the identified relationships between kallikrein and hemodynamic parameters provide additional insight into its physiological significance. The positive correlation with left ventricular ejection fraction indicates that decreased systolic function is accompanied by reduced kallikrein activity. Similarly, the association with the E/A ratio suggests a link between kallikrein and diastolic function, underscoring its involvement not only in biochemical but also in functional cardiac processes [13,19,20].

Despite these findings, several limitations of the study should be acknowledged. First, the single-center design and relatively limited sample size may restrict the generalizability of the results. Second, the potential influence of concomitant medications (such as ACE inhibitors, angiotensin receptor blockers, and diuretics) and comorbid conditions (e.g., diabetes mellitus) was not comprehensively evaluated, which may have affected the observed associations. Third, the absence of multivariate analysis precluded identification of independent prognostic factors. Additionally, the lack of long-term follow-up limits the ability to draw definitive conclusions regarding the prognostic value of kallikrein.

Future studies should include larger, multicenter cohorts and incorporate longitudinal follow-up to better define the clinical utility of kallikrein as a diagnostic and prognostic biomarker in cardiorenal syndrome.

Conclusion

1. A significant association was identified between decreasing kallikrein levels and increasing severity of cardiorenal syndrome in patients with chronic heart failure.

2. The observed inverse correlations between kallikrein and both NT-proBNP and aldosterone reflect an imbalance between neurohumoral regulatory systems and indicate a more advanced disease state.

3. The positive relationship between kallikrein and renal function parameters, particularly glomerular filtration rate calculated based on cystatin C, confirms its diagnostic relevance in the early detection of renal dysfunction.

4. The association of kallikrein with both systolic and diastolic cardiac function suggests its involvement in hemodynamic regulation in addition to biochemical processes.

5. The combined assessment of kallikrein, NT-proBNP, and cystatin C may provide substantial clinical value for early diagnosis and prognostic stratification of cardiorenal syndrome.

6. Integrating kallikrein measurement with established biomarkers such as NT-proBNP and cystatin C could improve early detection and risk stratification of cardiorenal syndrome in clinical practice.

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