



Serum copeptin level in contrast-induced nephropathy

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ARTICLE INFO

Article Type:
Original

Article History:

Received: 9 Dec. 2023

Accepted: 8 Jul. 2024

Published online: 17 Dec. 2025

Keywords:

Copeptin, Contrast-induced nephropathy, Percutaneous coronary intervention, Serum copeptin level, GFR, Serum creatinine

ABSTRACT

Introduction: The incidence of contrast-induced nephropathy (CIN) among patients who have undergone coronary angiography is about 10%-15%. According to the recent studies, copeptin might be a potential biomarker to predict the outcomes of adverse cardiac and renal events.

Objectives: This study aimed to assess the association between serum copeptin levels and CIN.

Patients and Methods: In this cross-sectional study a total of 75 candidates of percutaneous coronary intervention (PCI) or angiography were enrolled. A 12-lead ECG was recorded. The blood sample test was taken daily to identify changes in serum creatinine levels. CIN was defined as a 25% or 44 $\mu\text{mol/L}$ increase in serum creatinine in comparison to baseline or an increase in serum creatinine level ≥ 0.3 mg/dL (24.6 $\mu\text{mol/L}$) within 48-72 hours after contrast medium administration. IBM SPSS version 26.0 was used for all statistical analyses at a level of statistical significance of $P < 0.05$.

Results: The 48-hour follow-ups after the procedure revealed increased blood urea nitrogen levels in 8% and increased serum creatinine levels in 5.33% of patients. There was no relation between CIN development and serum copeptin. Our result showed no statistically significant association of serum copeptin levels with serum creatinine elevation and glomerular filtration rate (GFR) changes. Although, copeptin levels at admission, as well as hyperlipidemia, were independent predictors of serum creatinine increases and GFR decrement.

Conclusion: In conclusion, the serum copeptin level could be introduced as a simple prognostic biomarker for serum creatinine elevation and GFR decrement after contrast medium administration during coronary angiography or PCI.

Implication for health policy/practice/research/medical education:

According to recent studies, copeptin might be a potential biomarker to predict the outcomes of adverse cardiac and renal events. Based on our study, the serum copeptin level could be introduced as a simple prognostic biomarker for serum creatinine elevation and GFR decrease after contrast medium administration during coronary angiography or PCI.

Please cite this paper as: Nikfarjam S, Ramezanzade E, Fakh-Mousavi SA, Bahram Mirzaei M, Ghanavati S, Salari A, Khedmatbin Dana M. Serum copeptin level in contrast-induced nephropathy. J Renal Inj Prev. 2026; 15(2): e32291. doi: 10.34172/jrip.2025.32291.

Introduction

Iatrogenic acute kidney injury (AKI) related to contrast-induced nephropathy (CIN) is a significant cause of concern for physicians(1). The incidence of CIN among patients who have undergone coronary angiography is about 10%-15%, and it could be up to 25% in ST-elevation myocardial infarction patients (2,3).

It is still unclear how CIN occurred, however a previous study suggested it results from a combination of hypoxic and toxic injury caused by reactive oxygen species (ROS)

(4). Medullary hypoxia results in ROS production, which increases oxidative stress due to decreased vascular oxygenation. ROS activated vasoconstrictive pathways (like angiotensin II) and decreased nitric oxide bioavailability (5-7). Moreover, contrast administration reduces renal flow by increasing vasoconstriction in the renal arteries (8).

According to recent studies, copeptin might be a potential biomarker to predict the outcomes of adverse cardiac and renal events (9,10). Moreover, copeptin level

was significantly associated with renal dysfunction in heart failure patients (11).

Objectives

This study aims to assess the association between copeptin levels and CIN among patients undergoing coronary angiography or percutaneous coronary intervention (PCI).

Patients and Methods

Study design and population

This cross-sectional study was conducted in the referral heart academic hospital in the north of Iran. A total of 75 patients eligible for PCI or angiography was prospectively enrolled in this study from March 2018 to March 2019.

The patients were selected for further investigation if they met all of the following criteria: (a) adults (older than 18 years old), (b) individuals who indicated coronary angiography or PCI procedure according to American Cardiology College (ACC)/American Heart Association (AHA) guideline (12).

Exclusion criteria: (a) clinical evidence of severe infection, (b) history of allergic reaction to contrast medium or exposure to contrast medium in the last 48 hours, (c) underlying chronic kidney disease (CKD) or end-stage renal disease (ESRD), or history of kidney transplantation, (d) prior coronary artery bypass surgery (CABG) or PCI in the last six months, (e) cardiogenic shock diagnosis, (f) pregnancy, (g) poor echocardiography view, (h) history of severe heart failure (left ventricular ejection fraction [LVEF] <35%), (i) concomitant use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and diuretics, (j) prior treatment with thrombolytic agents, (k) death within 48 to 72 hours after PCI. After applying inclusion and exclusion criteria, a total sample of 75 patients was registered to the study.

A 12 lead ECG was recorded immediately after admission, and a board-certified cardiologist interpreted it. The blood sample was taken at admission and daily during follow-ups to identify changes in serum creatinine level. All PCI candidates had taken 300 mg aspirin and 300 to 600 mg clopidogrel (based on attending physician discretion) before the procedure.

Contrast-induced nephropathy was defined as a 25% or 44 $\mu\text{mol/L}$ increase in serum creatinine in comparison to baseline or an increase in serum creatinine level ≥ 0.3 mg/dL (24.6 $\mu\text{mol/L}$) within 48-72 hours after contrast medium administration (13).

An experienced cardiologist carried out transthoracic echocardiography after the PCI procedure and estimated LVEF using the modified Simpson method.

Blood samples

Five milliliters of venous blood samples were obtained into a heparinized tube to perform biochemical analysis.

After centrifugation, samples were stored at $-20\text{ }^{\circ}\text{C}$, and the copeptin level was measured using a sandwich immunoluminometric assay, as reported in the by study Morgenthaler et al (14). Accordingly, blood urea nitrogen (BUN) and serum creatinine levels were determined by standard methods. The glomerular filtration rate (GFR) was calculated based on the Modification of Diet in Renal Disease (MDRD) formula (15).

PCI procedure and in-hospital follow-up

A board-certified interventional cardiologist performed all procedures via the femoral route. Non-ionic low osmolality contrast medium was administered intravenously. Once arterial anatomy was visualized, 100 U/kg heparin was administered for patients. Patients' management was continued at the post-angiography unit. The decision to use antiplatelet agents, statins, ACE inhibitors, and beta-blockers was made based on the discretion of the attending physician and American College of Cardiology/American Heart Association guideline (16). Intravenous isotonic saline solution was prescribed for patients with no history of congestive heart failure. In addition, oral fluid ingestion was begun for patients with stable general status 90 minutes after the PCI procedure. Continuous monitoring of blood pressure, electrocardiography, and pulse oximetry were performed. Serum creatinine level was measured 48 hours after the procedure. During the study administration of nephrotoxic agents and non-steroidal anti-inflammatory medication were avoided.

Statistical analysis

Categorical variables were described using descriptive statistics such as frequency, and continuous variables were summarized as mean \pm standard deviation or median (interquartile range). A Kolmogorov-Smirnov test was used to determine the normality of the data, and the Levene test was used to assess the homogeneity of variances. A comparison of categorical variables was performed by chi-square test or Fisher's exact test. Independent *t* test or Mann-Whitney U test determined the difference between two continuous variables. Multilinear regression was conducted to evaluate the simultaneous effects of independent variables on the study outcomes. IBM SPSS Statistics for Windows; version 26.0 was used for all statistical analyses at a level of statistical significance of $P < 0.05$.

Results

The final analysis included 75 patients (mean age 56.09 ± 10.02 years, 49.3% female). Both age and gender had no statistically significant relationship with copeptin levels. The most common underlying disease was hypertension, followed by diabetes. Diabetes and copeptin levels exhibited a significant association (mean copeptin level 1.04 ± 0.54 pmol/L, $P = 0.013$) in univariate analysis.

Based on patients' medical histories, 27 patients (36%)

smoked cigarettes, and 18 patients (24%) used opium. There was a significant correlation between opium abuse and copeptin levels (mean copeptin level 1.16 ± 0.28 pmol/L), however no significant association was found between opium abuse and serum creatinine increase ($P=0.748$). An overview of the demographics and laboratory results of all sampled populations is shown in Table 1.

There were 19 PCI procedures performed (25.3%), 56 coronary angiographies (74.4%), and 15 cases (20%) that were CABG candidates after coronary angiography.

The 48-hour follow-ups after the procedure revealed increased BUN levels in six patients (8%) and increased serum creatinine levels in 4 patients (5.33%). All four patients who had increased serum creatinine levels

met the CIN criteria, since no correlation between CIN development and copeptin was found (mean copeptin level 1.12 ± 0.48 pmol/L, $P=0.814$).

The univariate analysis showed no statistically significant association of copeptin levels with serum creatinine elevation and GFR decrement (Table 1).

Still, the multivariate analysis results showed that copeptin levels at admission, as well as hyperlipidemia, were independent predictors of serum creatinine increases and decreased GFR (Table 2).

Discussion

Our findings demonstrated the role of copeptin level at admission as an independent predictor of rising serum creatinine and decreasing GFR, however there

Table 1. Association of serum copeptin level with baseline characteristics of patients, laboratory findings, and outcomes

Variable	Value	P value
Age (mean \pm SD) (y)	56.09 \pm 10.02	0.746
Female gender, n (%)	37 (49.30)	0.296
Current Smoker, n (%)	27 (36.0)	0.114
Opium user, n (%)	18 (24.0)	0.008
Diabetes, n (%)	27 (36.0)	0.013
Hyperlipidemia, n (%)	23 (30.70)	
Hypertension, n (%)	40 (53.30)	0.328
Previous Coronary angiography, n (%)	14 (18.67)	0.775
BMI, kg/m ² (mean \pm SD)	26.08 \pm 3.95	0.515
SBP, mmHg (mean \pm SD)	111.08 \pm 19.47	
DBP, mmHg (mean \pm SD)	70.60 \pm 10.64	
LVEF, mean \pm SD (%)	47.33 \pm 7.86	
Performed procedure		0.942
Coronary angiography, n (%)	56 (74.70)	
PCI, n (%)	19 (25.30)	
Drugs		
ACE inhibitors, n (%)	2 (2.67)	0.366
ARBs, n (%)	30 (40.0)	0.455
Potassium-sparing diuretics, n (%)	3 (4.0)	0.605
Laboratory findings		
BUN mg/dL – first day (mean \pm SD)	17.07 \pm 4.87	0.272
BUN mg/dL – 48 hours after the procedure (mean \pm SD)	18.31 \pm 4.26	0.912
Serum creatinine mg/dL – first day (mean \pm SD)	1.07 \pm 0.14	0.097
Serum creatinine mg/dL – 48 hours after the procedure (mean \pm SD)	1.13 \pm 0.17	0.594
Serum creatinine rise (%) (mean \pm SD)	5.76 \pm 10.09	0.191
eGFR mL/min/1.73 m ² - first day (mean \pm SD)	76.16 \pm 21.29	0.862
eGFR mL/min/1.73 m ² - 48 hours after the procedure (mean \pm SD)	72.23 \pm 19.61	0.913
eGFR decreased (%) (mean \pm SD)	-4.56 \pm 9.55	0.191
Copeptin pmol/L	1.08 \pm 0.40	

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, LVEF: Left ventricular ejection fraction, PCI: Percutaneous coronary intervention, ACE: Angiotensin II converting enzyme, ARB: Angiotensin receptor blocker, BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate.

Continuous variable described as mean \pm SD and categorical variable described as n (%).

Table 2. Multivariate analysis of potential predictor factor of creatinine raises and GFR reduction

Outcome	Predictor	Unstandardized coefficients		Standardized coefficients	P value	95% Confidence interval	
		B	Standard error	B		Lower	Upper
Serum creatinine raise (%)	Copeptin	-5.942	2.807	-0.239	0.038	-11.542	-0.343
	Hyperlipidemia	7.676	2.480	0.349	0.003	2.729	12.623
GFR reduction (%)	Copeptin	6.282	2.663	0.267	0.021	0.971	11.594
	Hyperlipidemia	-6.602	2.352	-0.318	0.007	-11.295	-1.909

was no association between copeptin levels and CIN development. This result contrasts with previous findings in the study by Yildirim et al (17), that demonstrated serum copeptin level was an independent predictor of CIN progress in ST-elevation myocardial infarction patients. Moreover, a community-based cohort study showed an independent positive association of plasma copeptin level and progression to CKD in individuals with underlying kidney disease as well as the general population (18). Another study suggested copeptin level as a prognostic factor for intermediate-term mortality in patients who suffer from kidney and coronary artery disease (19). The study on regular hemodialysis patients showed an elevation in the copeptin level before dialysis and reported a positive correlation between the copeptin level and fluid body volume. Furthermore, they declared the copeptin level depletion during hemodialysis (20). The discrepancy in the results seems to be due to the small sample population of the current study.

The result of the present study showed an association between copeptin level and underlying diabetes. A previous cross-sectional study among type 1 diabetes patients showed that serum copeptin strongly correlated with diabetic kidney disease and coronary atherosclerosis (21). Additionally, studies on type 2 diabetes patients reported that serum copeptin level was an independent predictor for diabetic nephropathy development (22-24). Previously, the study by Noor et al (25) showed plasma copeptin level was strongly associated with diabetes and renal biomarkers; moreover, patients with a positive family history of diabetes had a significantly higher copeptin level. Therefore, serum copeptin level might be a potential biomarker for predicting renal function impairment in patients at risk for renal injury development (26).

Based on the result of our study, hyperlipidemia was an independent predictor for serum creatinine elevation and GFR decline. Kidney function declines with age; diabetes and hyperlipidemia amplify it (27). In patients with underlying diseases such as anemia and CKD, statin therapy in various settings (ACS or elective PCI) showed clinical benefits in preventing CIN and reducing cardiovascular events (28). Statin therapy has been shown to reduce the risk of CIN development in patients with type 2 diabetes undergoing angiography or PCI (29-32). Statins at high doses and potency may exert renoprotective

effects by suppressing renal tubular cell apoptosis (33). However, the preventive effects of statins on CIN are not fully understood. Still, it is unknown whether they work through reducing oxidative stress and anti-inflammatory impacts or by lowering hyperlipidemia (34).

In our study, plasma copeptin levels and opium abuse were significantly associated but, the correlation between opium abuse and serum creatinine level elevation was not significant. In the cohort study evaluating the risk factor for AKI following isolated CABG, opium provided protection from AKI development. It may be due to the non-synthetic opium's antioxidant properties (35). To our knowledge, this is the first study to have found such an association between copeptin levels and opium abuse; additional multicenter studies are necessary to confirm the findings.

Conclusion

The present study results show that the serum copeptin level could be introduced as a simple prognostic biomarker for serum creatinine elevation and GFR decrease after contrast medium administration during coronary angiography or PCI. Still, more studies are needed to investigate the prognostic role of copeptin in CIN development.

Limitations of the study

We are aware that our study had two limitations. First, this was a single-center study, and results may differ in a larger population. Secondly, this study did not include a re-measure of copeptin level after the procedure and reversal of CIN. Thus, further multi-center study with a larger sample population is recommended.

Acknowledgments

We wish to thank the ethics committee of Guilan University of Medical Sciences and all the people who contributed to the completion of this study.

Authors' contribution

Conceptualization: Salman Nikfarjam, Elham Ramezanzade.

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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Guilan University of Medical Sciences (Ethical code#IR.GUMS.REC.1398.411). Prior to any intervention, all participants provided written informed consent. The study was extracted from Sahar Ghanavati's Cardiology thesis in the Department of Cardiology at this university. The authors have fully complied with ethical issues, such as plagiarism, data fabrication, and double publication.

Funding/Support

This research received no specific grant from anywhere.

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