

Significance of Cystatin C for Early Diagnosis of Contrast-Induced Nephropathy in Iraqi Patients Undergoing Coronary Angiography

Zahraa Malik Abood, Manal Kamal Rasheed, Haider Hamza Omran¹

Department of Biochemistry, College of Medicine, Baghdad University, Baghdad, ¹Department of Ministry of Health and Environment /Marjan Medical City, Hilla, Iraq

Abstract

Background: Contrast-induced nephropathy (CIN) has been traditionally defined as an increase in serum creatinine (sCr) after contrast media (CM) exposure. It is generally a transient and reversible form of acute renal failure. **Objectives:** The objective was to compare changes in serum creatinine and serum cystatin C (sCys C) in patients undergoing CM administration during coronary angiography (CAG) and/or intervention, and whether these changes are a reliable index for early identification of CIN. **Materials and Methods:** In this prospective study, 50 patients were included, 9 of them were omitted, and remaining 41 patients undergoing CAG and/or intervention. sCr, serum urea, sCys C, and estimated glomerular filtration rate (eGFR) were evaluated at baseline as well as 24 h after exposure to CM. **Results:** Forty one patients, six of them develop CIN (CIN group) and the remainder 35 not develop CIN (non-CIN group). Clinical parameters showed no significant association between CIN group and non-CIN group except in diabetes mellitus. As comparing patients before and after catheterization, the CIN group showed increase in sCr and serum urea, while remain nearly the same for sCys C, and obvious decrease for eGFR1 and eGFR2, in addition there is significant association for sCr, eGFR1, and eGFR2. In the non-CIN group, only the serum urea showed significant difference. **Conclusion:** The concentration change of sCr is significantly superior to cystatin C as an early biomarker in the CIN detection. An absolute increase of the concentration of sCr is highly sensitive and specific for the CIN in comparing to cystatin C.

Keywords: Contrast-induced nephropathy, coronary angiography, serum creatinine, serum cystatin C, serum urea

INTRODUCTION

Contrast-induced acute kidney injury (CI-AKI) or contrast-induced nephropathy (CIN) is generally considered as type of AKI that occurs after administration of parenteral contrast media (CM) within a narrow time interval.^[1]

The development of medical imaging technology and interventional radiology always be associated with complications such as CIN, which regards the third most common cause of hospital-acquired AKI.^[2] Coronary angiography (CAG) was used as diagnostic or percutaneous coronary intervention (PCI) as therapeutic purposes and use of intra-arterial contrast medium which is an iodinated diagnostic contrast used for optimizing the blood vessel visibility, which is predominantly excreted in the urine in patients with normal renal function, It is predominantly excreted in the urine.^[3]

An increase serum creatinine (sCr) level or decrease in urine output is the current gold standard for recognizing CIN. But sCr is insensitive to rapid acute reductions in kidney function, which may deteriorate more than 50% before sCr exceeds the normal range and it is influenced by a variety of nonrenal factors.^[4,5]

Serum Cystatin C (sCys C) is considered to be a more reliable marker than sCr in evaluating the glomerular filtration rate (GFR) in patients with acute renal failure during the first 24–48 h. Furthermore, growing evidence suggests that sCys

Address for correspondence: Dr. Zahraa Malik Abood,
Department of Biochemistry, College of Medicine, Baghdad
University, Baghdad, Iraq.
E-mail: malikzahraa@yahoo.com

Submitted: 26-Nov-2020 Accepted: 05-Dec-2020 Published: 29-Sept-2021

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How to cite this article: Abood ZM, Rasheed MK, Omran HH. Significance of cystatin C for early diagnosis of contrast-induced nephropathy in Iraqi patients undergoing coronary angiography. Med J Babylon 2021;18:191-4.

Access this article online

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DOI:
10.4103/MJBL.MJBL_88_20

C is a stronger predictor of clinical outcomes associated with chronic kidney disease (CKD) than sCr.^[6]

CIN is often considered a reversible and had a temporary course in clinical practice; Concentrations of sCr return to normal in up to 80% of cases after an average of 1–3 weeks.^[7]

The aims of the present study are comparing changes in sCr and sCys C in patients undergoing CM administration during CAG and/or intervention, and whether these changes in their concentration at 24 h after CM exposure is a reliable index for early identification of CIN.

MATERIALS AND METHODS

This study is a prospective type; 50 patients were included, 9 of them were omitted because of one or more of the next exclusion criteria, remaining 41 consecutive patients undergoing CAG and/or intervention who attended Shaheed AL-Mehrab Cardiology Center in the Marjan Medical City in Babylon government during the period from January to April 2019.

The criteria for inclusion in the study were as follows: patients aged 31–80 years, who had indication of CAG and/or PCI, and patients who gave voluntary permission for participation in this study. While the exclusion criteria involve: (1) patients with CKD (stage 2–4 CKD), (2) exposure to iodinated contrast within 1 week, or potential nephrotoxic drugs exposure, (3) previos renal transplants, heart disease, thyroid dysfunction, or cancer.

Age, gender, smoking, body mass index, left ventricular ejection fraction (<50%), history of diabetes mellitus, hypertension or chronic illness, history of kidney disease and medications (angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, beta-blocker, calcium channel blocker, and statin), and history of recent CM exposure are reported for every hospitalized patient.

The serum concentration of creatinine, urea, and sCys C was evaluated at baseline as well as 24 h after exposure to CM. sCr was measured enzymatically by the use of Reflotron® Plus Clinical Chemistry Analyzer, whereas the technique of enzyme-linked immunosorbent Assay (BioTek™ EL × 800™ Absorbance Microplate Readers) was used to measure sCys C. Baseline and 24 h postcatheterization are measured for estimated GFR (eGFR) calculated by online eGFR calculator by the National Kidney Foundation guideline.^[8]

- **For female:** “eGFR (mL/min/1.73 m²) = 144 – (Cr/61.6)^{-1.209} × (0.993) age”
- **For male:** “eGFR (mL/min/1.73 m²) = 141 × (Cr/79.2)^{-1.209} × (0.993) age.”

CIN is defined as an elevation of sCr of more than 25% or ≥ 0.5 mg/dl (44 μmol/l) from baseline within 48 h of CM exposure,^[9] which is widely accepted formula by the European Society of Urogenital Radiology.

The study was approved by the ethics committee of our institution, and all participating patients provided verbal informed consent.

All statistical analysis was using Statistical Package for the Social Science (SPSS) (SPSS version 22 software): IBM Software Group, ATTN: Licensing, 200 W. Madison St., Chicago, IL; 60606, U.S.A. Continuous data were expressed as means ± standard deviation (SD). Categorical variables are presented as absolute numbers and percentages. Comparison of continuous variables was analyzed using paired *t*-tests and the Student's *t*-test if the data are normally distributed. If the data are not normally distributed, nonparametric testing analyzed differences. Categorical variables were analyzed with Pearson's Chi-square test. Statistical significance was considered whenever $P \leq 0.05$.

Ethical consideration

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The study was carried out with patients' verbal and analytical approval before the sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee (Babil health directorate).

RESULTS

The results show that the total patients (41) are divided in to CIN group (6 patients, with incidence 14.63%) and non-CIN group (35 patients). Thirty-three of them were men and eight were women, so male-to-female ratio (4:1) and age range included was between 18 and 80 years

The age presentation shows that CIN group with mean age of 61.33 ± 12.28 years is older than non-CIN group with mean age of 56.74 ± 11.27 years, and all of the CIN patients were male and diabetic patients, also all of them did PCI. Other clinical parameters such as hypertension, diabetes mellitus, smoking habits, and past drug history were found 33.3%, 100%, 50%, and 66.7% in CIN group, respectively, in compare to 44.1%, 35.3%, 47.1%, and 47.1% in non-CIN group respectively, and these all clinical parameters show no significant association between CIN group and non-CIN group except in diabetes mellitus with highly significant association ($P \leq 0.001$). All these clinical characteristics are illustrated in Table 1.

In non-CIN group, there is increasing in the mean ± SD for sCr (but <0.5 mg/dl) and serum urea after contrast medium administration (which are 1.13 ± 0.29 mg/dl, 36.08 ± 8.18 mg/dl) respectively as compared to those before catheterization (1.06 ± 0.29 , 32.83 ± 6.88) mg/dl, while for sCys C remain approximately the same (0.75 ± 0.33 , 0.78 ± 0.44 mg/dl before and after catheterization, respectively) and decrease for eGFR1 and eGFR2 (76.20 ± 18.48 , 94.23 ± 27.23 before and 71.5 ± 18.84 , 90.44 ± 28.77 after/orderly), and also only the serum urea showed significant association $P = 0.000$ while

Table 1: Clinical basal characteristics for contrast-induced nephropathy and noncontrast-induced nephropathy groups

The parameter	CIN (n=6), n (%)	Non-CIN (n=35), n (%)	P
Age (years), mean±SD	61.33±12.27	56.73±11.27	0.422***
Male	6 (100)	26 (76.5)	0.084**
Female	0	8 (22.8)	-
BMI, mean±SD	24.96±4.56	25.60±4.81	0.495****
Hypertension	2 (33.3)	15 (44.1)	0.21**
Diabetes mellitus	6 (100)	12 (35.3)	0.001*
Smoking habits	3 (50)	16 (47.1)	0.761**
PCI done	6 (100)	31 (88.57)	0.424**
CAG done	0	21 (60)	-
Past medical history	4 (66.7)	16 (47.1)	0.061**

*Significant P, **Chi-square test, ***Independent sample t-test, ****Mann-Whitney U. BMI: Body mass index, CIN: Contrast-induced nephropathy, CAG: Coronary angiography, PCI: Percutaneous coronary intervention, SD: Standard deviation

Table 2: Compare association within (before and after catheterization) each group of contrast-induced nephropathy and noncontrast-induced nephropathy regarding serum creatinine, serum cystatin C, and serum urea

The parameter	Mean±SD		P
	Before catheterization	After catheterization	
Non-CIN (n=35)			
Serum creatinine	1.068±0.29	1.129±0.29	0.247
Serum cystatin C	0.75±0.33	0.78±0.44	0.698
Serum urea	32.83±6.88	36.08±8.18	0.000*
eGFR1	76.20±18.48	71.5±18.84	0.222
eGFR2		90.44±28.77	0.449
CIN (n=6)			
Serum creatinine	1.122±0.32	3.05±2.08	0.049*
Serum cystatin C	0.794±0.35	0.71±0.401	0.568
Serum urea	34.75±7.92	60.33±50.42	0.24
eGFR1	73.83±22.63	32.16±19.13	0.001*
eGFR2	88.5±20.88	53.5±17.96	0.021*

*Significant P (P≤0.05) by paired sample t-tests. eGFR1 calculated by CKD-EPI creatinine in (mL/min/1.73 m²). eGFR: Estimated glomerular filtration rate, CKD-EPI: Chronic kidney disease-epidemiology collaboration, CIN: Contrast-induced nephropathy, SD: Standard deviation

the other parameters (sCr, sCys C, eGFR1, and eGFR2) show no significant association (P≥0.05) when compared to before catheterization in the same group as illustrated in Table 2.

In the CIN group, there is observable increase in the mean ± SD ≥ 0.5 mg/dl for sCr and serum urea (from 1.122 ± 0.32 mg/dl to 3.05 ± 2.08 mg/dl for sCr and from 34.75 ± 7.92 mg/dl to 60.33 ± 50.42 mg/dl for serum urea), while remain nearly the same for sCys C (0.79 ± 0.35 and 0.71 ± 0.4 mg/dl), and obvious decrease for eGFR1 and eGFR2 (from 73.83 ± 22.63, 88.5 ± 20.88 to 32.16 ± 19.13, 53.5 ± 17.96 for them

orderly) as compared to before catheterization; in addition, there is significant association for sCr, eGFR1, and eGFR2 (P = 0.049, 0.001, 0.021), respectively, but the serum urea and sCys C show no association (P = 0.24, 0.568), respectively, as clarified in Table 2.

DISCUSSION

Six patients out of the total 41 patients included in our study developed CIN (n = 6) and the remaining patients considered as non-CIN (n = 35), accordingly, this study concluded a 14.63% CIN incidence in patients undergoing CAG and/or intervention which is comparable to earlier studies whose authors showed a incidence of CIN spanning from 5% to 15% in patients experience contrast-related procedures.^[10]

The risk of CIN development is elevated in elderly and diabetic patients attributable to endothelial dysfunction and excessive vasoconstrictive responsiveness to CM,^[11] and this fact agrees with our study as we found that all CIN patients were diabetic (100% CIN incidence) with highly significant association (P≤0.0001) and older than non-CIN patients (with a mean age of 61.33 ± 12.275 vs. 56.735 ± 11.2743 for non-CIN).

The study found that CIN incidence in the male patients was greater than that in the female (100% in male vs. 0% in female), meaning that all CIN patients were male, but had not reached statistically significant results between CIN and non-CIN (P ≤ 0.084), this could be attributed to small number of female in our study compared to male, be explained by the fact that male sex being considered as nonmodifiable risk factor for coronary heart disease.

Another important observation of the present study is that patients with PCI had a higher incidence of CIN (100%) than patients who did diagnostic CAG only (0%) as they receiving a higher CM dose, but statistically insignificant (P ≤ 0.424) probably because most of the included patients in our research did PCI. A similar observation was noted by Brown *et al.* who found that people who took CM amounts greater than the calculated dosage have a higher occurrence rate of CIN.^[12]

In this study, when comparing precatheterization (baseline) and postcatheterization (after 24 h CM exposure) sCys C and sCr values in the CIN group, found that sCys C level did not rise after 24 h of CM introduction whereas sCr at 24 h had significant rise as compared to baseline (P ≤ 0.049), which consistent with the study of Ribichini *et al.*: documented that sCr changes from base point provide stronger diagnostic accuracy able to predict CIN in an early stage than comparable changing patterns in sCys C.^[13]

Although sCr is an insensitive indicator during acute changes in renal function,^[14] conversely, in the present work, sCr was obviously superior to sCys C.

Although, recently, sCys C was proposed as an alternative to sCr for diagnosing AKI^[15,16] and the reliability of sCys C as a biomarker in detecting acute changes in kidney

function has been proven in several previous studies,^[17] these recommendations disagree with our conclusions.

CONCLUSION

The current study found that the concentration change of sCr is significantly superior to cystatin C as an early biomarker in the CIN detection. An absolute increase of the concentration of sCr is highly sensitive and specific for the CIN prediction at 24 h following exposure to iodinated contrast medium in comparing to cystatin C.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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