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# Urinary trehalase activitiy in contrast-associated acute kidney injury

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**Abstract. – OBJECTIVE: Contrast-associated acute kidney injury (CA-AKI) is the third most common cause of hospital-acquired AKI. Sensitive biomarkers can detect kidney injury early on because kidney damage begins immediately after the administration of a contrast medium. Due to its proximal tubule specificity, urinary trehalase can be a useful and early marker for detecting tubular damage. This study aimed to reveal the power of urinary trehalase activity in diagnosing CA-AKI.**

**PATIENTS AND METHODS: This is a prospective, observational, and diagnostic validity study. The study was performed in an academic research hospital's emergency department. Patients aged 18 years and over who underwent contrast-enhanced computed tomography in the emergency department were included in the study. Urinary trehalase activities were measured before and 12, 24, and 48 hours after the administration of a contrast medium. The primary outcome was the occurrence of CA-AKI, while the secondary outcomes were risk factors for CA-AKI, duration of hospital stay after contrast use, and the mortality rate in the hospital.**

**RESULTS: A statistically significant difference between the CA-AKI group and the non-AKI group was found in the activities measured 12 hours after the administration of the contrast medium. Notably, the mean age of the patient group with CA-AKI was considerably higher than that of the non-AKI group. The risk of mortality was found to be remarkably more elevated in patients with CA-AKI. Further, there was a positive correlation between trehalase activity and HbA1c. In addition, a crucial correlation was found between trehalase activity and poor glycemic control.**

**CONCLUSIONS: Urinary trehalase activity can be useful as a marker of acute kidney injuries due to proximal tubule damage. In the diagnosis of CA-AKI, especially the activity of trehalase in the 12th hour might be useful.**

*Key Words:*
Contrast-associated acute kidney injury, Post-contrast acute kidney injury, Diabetic nephropathy, Trehalase.

## Introduction

Contrast-associated acute kidney injury (CA-AKI) is a type of acute kidney injury (AKI) that occurs following exposure to a contrast medium (CM). It is the third most common cause of hospital acquired AKI[1]. The incidence of CA-AKI is 2% in the general population, but it rises to 50% in patients with multiple risk factors[2]. Significant risk factors for CA-AKI are advanced age, hypotension, female sex, diabetes, heart failure, chronic kidney disease, and anaemia[3]. In patients with risk factors, the mortality rate associated with CA-AKI reaches up to 34%[4]. CA-AKI is caused by multiple factors, such as intrarenal vasoconstriction, reactive oxygen radicals, and direct tubular damage[5].

For more than 100 years now, serum creatinine (sCr) has been used in clinical practice to diagnose AKI[6]. However, sCR is an unreliable marker for AKI because it is affected by non-renal factors such as age, gender, muscle mass, muscle metabolism, drugs, hydration status, nutritional status, and tubular secretion[7]. Despite these known limitations, AKI discussion in the literature continues to use the sCr level as the diagnostic standard because there is no alternative marker[8].

In patients with normal renal function, the half-life of iodinated CM is approximately 2 hours after the intravenous (IV) injection. In the first 4 hours, 75% of the given CM is excreted with the



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urine, and 98% of the remaining CM leaves the body after 24 hours[9]. Serum creatinine level begins to increase 24-48 hours after CM exposure[10].

Because kidney damage starts immediately after the CM administration, sensitive biomarkers are likely to detect kidney damage remarkably early on[11]. In recent years, several biochemical markers have been studied[12] as sensitive and specific biomarkers capable of detecting acute tubular injury early on. Some of these biomarkers include N-acetyl-β-D-glucosaminidase (NAG), neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), cystatin C, IL-18, and proximal tubule brush border enzymes.

Trehalase is an enzyme with a molecular weight of 75 kDa and is expressed in the proximal renal tubule. Trehalase hydrolyzes trehalose is a disaccharide found mainly in insects, fungi, and plants, into two molecules of glucose[13]. Trehalase is specific to trehalose as a substrate. It is localized in the membrane of the proximal tubular brush borders. Due to its proximal tubule specificity and affinity for a single substrate, urinary trehalase can be a useful biomarker for detecting tubular damage[14,15].

There are several studies[15-17] on urinary trehalase activity in environmental toxin-induced AKI. However, there is only one study[18] on the evaluation of urinary trehalase levels in the diagnosis of CA-AKI, and it was done after intraarterial CM exposure. This study aimed to demonstrate the diagnostic value of urinary trehalase levels in the diagnosis of CA-AKI after IV exposure.

## Patients and Methods

### Study Design

This study is a prospective observational study of diagnostic validity. The study was performed between 15 November 2019 and 15 March 2020 in an Educational Research Hospital's Emergency Department, after the approval of the local Ethics Committee.

### Patient Population

Eighteen years and older patients who were performed contrast-enhanced computed tomography (CECT) in the emergency department were included in the intervention group. The control group was composed of patients with no exposure to CM. All participants provided informed consent. Approval of patients who could not give consent was obtained from their 1st-degree relatives. Patients who had insufficient medical data, no urine output, a history of a kidney transplant or dialysis, and who abandoned voluntarily were excluded from the study. The flow chart of the study is shown in Figure 1.

### Outcomes

The primary outcome was the occurrence of CA-AKI. The definition of CA-AKI was an increase in serum creatinine 25% or 0.5 mg/dL within 48 hours after contrast administration. Secondary outcomes were risk factors for CA-AKI, duration of hospital stay after contrast use, and mortality rate in the hospital.

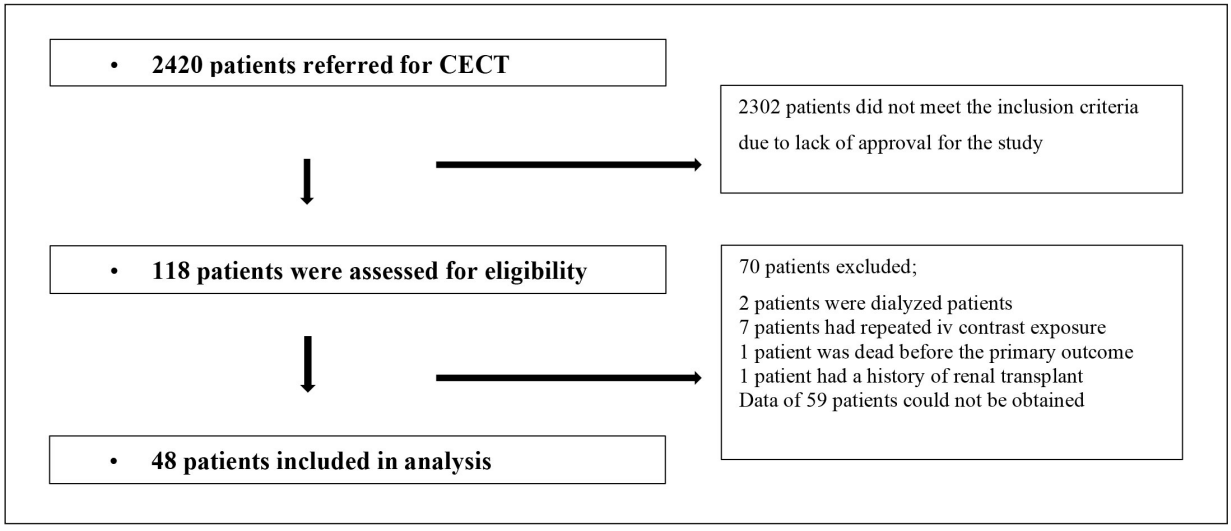


**Figure 1.** Flow chart for patient selection process.

### Data Collection

A prepared data collection form was used to collect data. Demographic data, vital signs, known comorbidities, blood urea nitrogen (BUN), glucose, and creatinine values during emergency department admission, BUN and creatinine values 48 hours after contrast exposure, and HbA1c values within three months were written to study forms. Urine samples were collected before the administration of CM and in 12$^{th}$ hour, 24$^{th}$ hour, and 48$^{th}$ hour after IV contrast exposure. The clinical endpoint was registered as discharge or death, the duration of hospital stays as days. Iohexol was used < 100 mL in all patients as a contrast medium.

### Sample Collection and Trehalase Measurement

The urine sample from the patients with a foley catheter was taken directly with a needle or syringe; from the patients without a catheter, a midstream urine sample was taken. The measurements were made as described in the Patent Cooperation Treaty (PCT), International Application Number: PCT/TR2021/051187. The samples were kept at +4°C for batch processing. The trehalase activity measurement principle was based on glucose measurement in the urine, after the breakdown of the trehalose by trehalase. First, glucose was measured in the urine sample. Glucose was measured again after adding 25 microL 40% trehalose solution (40 g trehalose/100 mL deionized water) to 975 microL urine and incubated at 37°C for 30 minutes. The difference between the two measurements was considered trehalase activity. Urine glucose was measured on a Beckman Coulter AU480 (Brea, CA, USA) device with a Beckman brand urinary glucose kit by the kinetic colorimetric method. Trehalose was purchased from Cargill.

### Group Analysis

For analysis of primary and secondary outcomes, patients were split into three categories:

1. CA-AKI group: Patients who developed CA-AKI after IV CECT.
2. No-CA-AKI group: Patients who did not develop CA-AKI after IV CECT.
3. NON-AKI group: Patients who were not exposed to CM (Control group) and patients without CA-AKI (No-CA-AKI group).

The CA-AKI group was compared with both groups; the No-CA-AKI and the NON-AKI.

### Statistical Analysis

For continuous variables, all statistical values were expressed as median and minimum-maximum or mean and standard deviation. Categorical variables were presented as percentages and absolute values. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to evaluate the normality of distributions. Mann-Whitney U test and *t*-test were used when comparing groups. For nominal (categorical) variables, the Chi-square test and Fisher's exact test were used. Spearman's rho test was used for nonparametric data in the correlation analysis. The area under the curve (AUC) for the receiver operating characteristic (ROC) curve was used to analyze the trehalase sensitivity and specificity for the occurrence of CA-AKI. A *p*-value lower than 0.05 was considered statistically significant. The statistical analyses were performed using a statistical software package SPSS, version 24 for Windows (IBM Crop., Armonk, NY, USA).

## Results

During the study period, 2,420 patients underwent IV CECT in the emergency department. Of these, 2,302 patients were excluded because they did not consent to the study. The remaining 118 patients were assessed for eligibility. Two of them were dialysis patients, seven had repeated IV CM exposure, one died before the manifestation of primary outcome during the study, one had a history of a renal transplantation, 59 patients were inaccessible for data collection; all these patients were excluded from the study (Figure 1). A total of 48 patients were included in the intervention group. Twenty-five patients without IV CM exposure were assigned to the control group. The intervention and control groups were similar in terms of demographic characteristics and vital signs.

The mean age of the CA-AKI group was considerably higher than the non-CA-AKI group. There was no significant difference between the two groups in terms of gender, vital signs, and comorbidities. Mortality was found significantly higher in patients with CA-AKI (Table I).

The urea and creatinine values of patients with CA-AKI were higher than those of the patients without CA-AKI at the 48$^{th}$ hour. Between the CA-AKI and the non-CA-AKI groups, urinary trehalase activities did not differ significantly. Urinary trehalase activity was significantly higher only at the 12$^{th}$ hour in the CA-A-

**Table I.** Demographic and clinical characteristics of Intervention and control groups.

| | Intervention group (n=48) | | | | | |
|---|---|---|---|---|---|---|
| | CA-AKI (n=9) | No CA-AKI (n=39) | p | Intervention group (n=48) | Control group (n=25) | p |
| Age (year) | 80.78±9.48* | 62.21±19.08* | **0.007** | 71 (18-96)¶ | 75 (23-89)¶ | 0.396 |
| Men: Women | 5:4 | 26:13 | 0.701 | 31:17 | 12:13 | 0.172 |
| SBP (mmHg) | 147±37* | 145±31* | 0.864 | 146±32* | 145 (110-250)¶ | 0.736 |
| DBP (mmHg) | 86±18* | 85±16* | 0.990 | 85±16* | 88±18* | 0.573 |
| Heart rate | 97±24* | 93±15* | 0.512 | 91 (62-136)¶ | 99±22* | 0.340 |
| Diabetes mellitus [n (%)] | 3 (33.3) | 14 (35.8) | 1.0 | 17 (35.4) | 9 (36) | 0.682 |
| Hypertension [n (%)] | 4 (44.4) | 17 (43.6) | 1.0 | 21 (43.8) | 7 (28) | 0.189 |
| Coronary artery dieases [n (%)] | 3 (33.3) | 8 (20.5) | 0.409 | 11 (22.9) | 8 (32) | 0.401 |
| Chronic kidney dieases [n (%)] | 1 (11.1) | 5 (12.8) | 1.0 | 6 (12.5) | 6 (24) | 0.208 |
| Heart failure [n (%)] | 2 (22.2) | 3 (7.7) | 0.231 | 5 (10.4) | 5 (20) | 0.258 |
| Baseline sCr (mg/dL) | 0.87 (0.56-1.71)¶ | 0.8 (0.48-2.36)¶ | 0.579 | 0.85 (0.48-2.36)¶ | 0.92 (0.39-2.33)¶ | 0.530 |
| Mortality [n (%)] | 5 (55.6) | 4 (10.3) | **0.007** | 9 (18.8) | 7 (28) | 0.365 |

CA-AKI: Patients with contrast associated-acute kidney injury; No CA-AKI: Patients without contrast associated-acute kidney injury; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; sCr: Serum creatinine; n: Number of subjects in the group; *mean ± standard deviation; ¶median (minimum-maximum).

**Table II.** Comparison of urinary trehalase activity with serum creatinine and urea in patients with and without CA-AKI.

| | CA-AKI (n=9) Median (min-max) | No CA-AKI (n=39) Median (min-max) | p | CA-AKI (n=9) Median (min-max) | NON-AKI (n=64) Median (min-max) | p |
|---|---|---|---|---|---|---|
| Urea ($0^{th}$ hour) | 54 (33-138) | 37 (21-141) | 0.068 | 54 (33-138) | 45 (19-238) | 0.392 |
| Urea ($48^{th}$ hour) | 68 (34-145) | 41 (11-131) | **0.030** | 68 (34-145) | 41 (11-131) | **0.030** |
| Creatinine ($0^{th}$ hour) | 0.87 (0.56-1.71) | 0.8 (0.48-2.36) | 0.579 | 0.87 (0.56-1.71) | 0.86 (0.39-2.36) | 0.737 |
| Creatinine ($48^{th}$ hour) | 1.26 (0.77-2.46) | 0.67 (0.42-2.64) | **<0.001** | 1.26 (0.77-2.46) | 0.67 (0.42-2.64) | **<0.001** |
| Trehalase ($0^{th}$ hour) | 4.7 (1.60-10.8) | 4.9 (0.70-117.2) | 0.398 | 4.7 (1.60-10.8) | 4 (0.2-117) | 0.663 |
| Trehalase ($12^{th}$ hour) | 7.9 (2.6-74.8) | 5 (0-327) | 0.066 | 7.9 (2.6-74.8) | 3.6 (0-327) | **0.010** |
| Trehalase ($24^{th}$ hour) | 5.8 (0.1-24.2) | 5.8 (0-215) | 0.625 | 5.8 (0.1-24.2) | 4.5 (0-215) | 0.675 |
| Trehalase ($48^{th}$ hour) | 3.6 (0.5-24.2) | 6.2 (0.3-301) | 0.597 | 3.6 (0.5-24.2) | 4.05 (0.2-301) | 0.585 |

Data expressed as median (minimum-maximum). CA-AKI: Patients with contrast associated-acute kidney injury patients; No CA-AKI: Patients without contrast associated-acute kidney injury; NON-AKI: Patients without any acute kidney injury; n: Number of subjects in the group; min: Minimum; max: Maximum.

KI group compared with the non-CA-AKI group (Table II).

In the ROC analysis of $12^{th}$ hour urinary trehalase activity in the CA-AKI group, the area under the curve was 0.776 (95% CI: 0.665-0.885). According to the Youden Index, when the threshold value was determined to be 4.7; the sensitivity was 88.89%, and the specificity was 60.94% (Figure 2).

There was no significant relationship between urinary trehalase activity and known comorbidities. There was a positive correlation between urinary trehalase activity and HbA1c. Urinary trehalase activity was found to be significantly high in patients with poor glycemic control in whom the HbA1c level was above 6.5 (Table III).

## Discussion

In recent years, with the increasing use of CECT for critical diagnosis in the emergency department, the occurrence of CA-AKI has also become an essential problem[19].

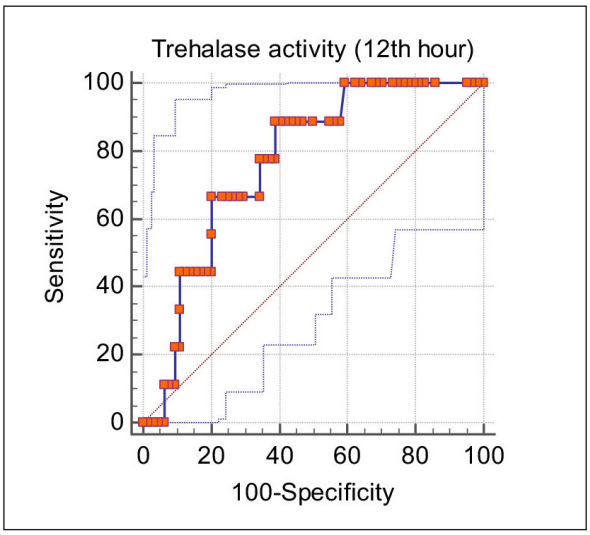


**Figure 2.** ROC curve of 12th hour urinary trehalase activity for contrast associated-acute kidney injury

A critical increase in urinary trehalase activity after exposure to lead and cadmium has been reported[16,17]. Urinary trehalase, an indicator of tubular damage is significantly higher in patients with nephrotic syndrome before treatment and decreases after therapy[20]. Proximal tubule brush border damage occurs following CM exposure. A similar type of damage can be caused by environmental toxins such as lead and cadmium which increase urinary trehalase[21]. Our study showed a significant increase in urinary trehalase activity after 12 hours of CM exposure, taking place sooner than that observed using the classical marker, serum creatinine. Thus, urinary trehalase might be useful for the early detection of acute tubular damage.

Some urinary enzymes were tested to detect nephropathy after arterial CM exposure.

Among these enzymes, urinary trehalase activity was the first to show a marked increase, peaking in some patients and reported[18] that urinary trehalase level was increased early, peaked in some patients on the same day and returning to baseline after 48 hours. In another study[15], after exposure to mercury chloride, urinary trehalase peaked at the 16th hour, and returned to baseline after 48 hours. Our study shows agreement with these previous studies; urinary trehalase activity increased at the 12th hour and decreased at the 48th hour after CM exposure in the CA-AKI group. Therefore, urinary trehalase activity at the 12th hour might be a promising marker for CA-AKI diagnosis.

A study reported[22] increased urine trehalase activity in patients with type II diabetes. It was higher in the early stages of diabetes when there was no evidence of proteinuria or glucosuria. In the later stages of diabetes, trehalase activity was reported[22] to decrease due to the loss of brush borders in the proximal tubules. In our study, no significant relationship between urinary trehalase activity and, blood glucose was found. In contrast, there was a positive correlation with HbA1c. Besides, urinary trehalase activity was found to be significantly high in patients with poor glycemic

**Table III.** Urinary trehalase activity in chronic disease and its correlations with glucose, urea, creatinine.

| | Trehalase 0th hour Median (min-max) | p | Trehalase 12th hour Median (min-max) | p | Trehalase 24th hour Median (min-max) | p | Trehalase 48th hour Median (min-max) | p |
|---|---|---|---|---|---|---|---|---|
| DM | 4.8 (0.4-117.2) | 0.060 | 7 (0.7-327) | **0.038** | 15 (0.1-215) | 0.068 | 5 (3-301) | 0.201 |
| Hyperglycemia | 4.9 (0.6-91) | 0.104 | 6.7 (2-327) | 0.202 | 15 (0.1-215) | 0.166 | 8.5 (0.5-301) | 0.185 |
| Poor glycemic control | 6.95 (0.7-91) | **0.003** | 11.3 (0.7-327) | 0.059 | 24 (0.1-215) | **0.040** | 14.5 (3.5-301) | **0.004** |
| CHF | 3.85 (0.4-35) | 0.804 | 7 (2.6-327) | 0.206 | 5.9 (0.1-113) | 0.826 | 6.7 (3.3-108) | 0.265 |
| CAD | 3 (0.3-91) | 0.628 | 5.2 (0-327) | 0.668 | 5.2 (0-113) | 0.951 | 14 (0.3-108) | 0.391 |
| CKD | 3.35 (0.2-75) | 0.552 | 4.4 (2.6-11.5) | 0.767 | 5.35 (4.3-12.6) | 0.988 | 3.95 (3.2-13) | 0.473 |
| Hypertension | 4.65 (0.4-91) | 0.158 | 4.9 (0.4-327) | 0.678 | 5.9 (0.1-215) | 0.383 | 5 (0.5-301) | 0.589 |
| | r | p | r | p | r | p | r | p |
| HbA1c | 0.491 | **0.004** | 0.555 | **0.004** | 0.551 | **0.004** | 0.477 | **0.016** |
| Glucose | 0.169 | 0.154 | 0.236 | 0.106 | 0.128 | 0.387 | 0.118 | 0.425 |
| Urea (48th hour) | -0.173 | 0.143 | 0.138 | 0.35 | -0.067 | 0.653 | 0.103 | 0.485 |
| Creatinine (48th hour) | 0.087 | 0.463 | 0.091 | 0.537 | -0.004 | 0.979 | -0.007 | 0.962 |

CAD: Coronary artery disease; CHF: Congestive heart failure; CKD: Chronic kidney disease; DM: Diabetes mellitus; Hyperglycemia: Blood glucose levels > 200mg/dL; r: Spearman's rank correlation coefficient; min: Minimum; max: Maximum.

control. This might be a sign of diabetic nephropathy. Therefore, urinary trehalase activity might be beneficial in the follow-up of nephropathy in patients with diabetes. There is a need for controlled studies on this subject in the selected patient group.

Factors such as advanced age (> 75 years), hypotension, female sex, diabetes, heart failure, chronic kidney disease, and anemia are among the main risk factors for CA-AKI[3]. Notably, in our study, no significant difference was found between the two groups in terms of risk factors such as sex, blood pressure, diabetes, heart failure, chronic kidney disease, coronary artery disease, cerebrovascular disease, and hyperglycemia. However, the mean age of the CA-AKI group was significantly higher. With age, a decrease in total kidney mass, tubule number and function, and kidney blood flow is observed[23]. Therefore, one can argue that advanced age is an independent risk factor for CA-AKI.

According to the guideline published by the Contrast Media Safety Committee of the European Society of Urogenital Radiology, CA-AKI incidence ranges from 5 to 6.4%. In their study on inpatients, Nash et al[1] reported the incidence of CA-AKI to be 11%. Similarly, our study also involved inpatients, in whom the frequency of CA-AKI was found to be 18%. This shows that the incidence of CA-AKI in inpatients is higher than in the outpatient group.

A study[24] reported a mortality rate of 34% in patients who developed CA-AKI during hospitalization and 7% in control patients who received CM but did not develop CA-AKI. In our study, the mortality rate was 55.6% in the CA-AKI group and 10.3% in the non-CA-AKI. In accordance with Levy et al[24] research, the mortality of the group with CA-AKI was crucially higher. Further, the mortality rate in the CA-AKI group was significantly higher. Thus, it can be said that the development of AKI is a critical risk factor for mortality.

### Limitations

This study is a single-center prospective study conducted in the emergency department. Because the patients in the emergency department were difficult to follow-up for 48 hours, the number of patients in the study was limited and may have affected the study's strength. Besides, this led to the inclusion of only hospitalized patients. Because of this, the intervention group comprised patients of advanced age and with concomitant chronic diseases; consequently, the mortality rates might have been affected. In the subgroup analysis of the study, a significant relationship was found between urinary trehalase activity and HbA1c. Although, urinary trehalase activity in the patients with CA-AKI might have been affected by their poor glycemic control.

## Conclusions

Urinary trehalase activity can be useful as a marker of acute kidney injuries due to proximal tubule damage. In the diagnosis of CA-AKI, urinary trehalase activity at the 12$^{th}$ hour might be a promising marker. The diagnostic accuracy study of urinary trehalase activity for CA-AKI can be performed by excluding the diabetic patient group.

Further, a positive correlation between urine trehalase activity and HbA1c was found. Thus, this enzyme might be useful in screening and diagnosing diabetic nephropathy. However, there is a need for comprehensive controlled studies on this subject in the selected patient groups.

Advanced age is an independent risk factor for CA-AKI. Even if there is no other risk factor for CA-AKI, caution is required before applying CM in older people.

In addition, mortality is significantly higher in hospitalized patients with CA-AKI. The development of AKI in inpatients might indicate an increased risk of mortality. Therefore, patients who develop CA-AKI should be considered critical.

### Conflict of Interest

All authors declare no conflict of interests.

### Ethics Approval

The study was conducted in accordance with the ethical standards of the Helsinki Declaration and was approved by the Local Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital.

### Informed Consent

Informed consent was obtained from all individual participants included in the study.

### Funding

This research received no external funding.

### Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author.

### Authors' Contributions

BK: methodology, investigation, data curation, writing - original draft; HD: conceptualization, methodology, formal analysis, writing - review and editing; AO: conceptualization, resources, writing - review and editing; AK: investigation, resources; YY: formal analysis, writing - review and editing, STN: investigation, resources.

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