IGFBP7 is a predictor of diuretic-induced acute kidney injury in the patients with acute decompensated heart failure

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Abstract

Objectives: The serum Insulin-like growth factor-binding protein 7 (IGFBP7) levels were tested to predict acute renal damage that may develop in patients with stage III–IV heart failure who were treated with intravenous diuretics in the emergency department.

Method: Patients with stage III–IV heart failure (n=84) were included in this prospective observational study. All patients were treated with IV diuretic therapy in accordance with a predetermined protocol. The serum IGFBP7 and creatinine levels were analyzed at the beginning of the treatment (0 h), 6th, and 12th hours. The creatinine level and glomerular filtration rate (GFR) at baseline were compared with the 12th hour values. The results were classified according to the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) criteria for each patient. The patients were divided into two groups as those in any RIFLE group (RIFLE (+)) and those without (RIFLE (−)). The groups were compared in terms of IGFBP7 levels.

Results and Discussion: 0, 6th, and 12th hour levels of IGFBP7 were significantly different between the RIFLE + and RIFLE − groups. (p=0.036, 0.042, and 0.006, respectively). The IGFBP7 levels were higher in RIFLE (+) group. However, the IGFBP7 values did not increase with time. In the ROC curve analyze for IGFBP7 levels, the cutoff with the highest sum of sensitivity (0.80) and specificity (0.69) was 118.71.

Conclusions: The serum IGFBP7 levels can predict the risk of developing AKI before the diuretic treatment in the patients with stage III–IV heart failure.

Keywords: acute kidney injury; diuretic; heart failure; IGFBP 7; RIFLE.

Introduction

Hospitalization is critically important for acute decompensated heart failure (ADHF) owing to the associated high risk for acute kidney injury (AKI). This condition is categorized under a spectrum of disorders called cardiorenal syndrome. Monotherapy with a diuretic has been shown to improve patients’ condition; however, these diuretics can cause AKI by affecting the renal filtration rate in different ways. AKI leads to increased morbidity and mortality. Early diagnosis is very important owing to the need for prolonged hospitalization and increased treatment costs [1–4].

It is very important to detect kidney damage in the preclinical process with new diagnostic methods and thus to provide early intervention in AKI. Therefore, it is necessary to search for new biomarkers that can be detected in serum or urine at an early stage before the creatinine value rises [1–4].

IGFBP7 (insulin-like growth factor-binding protein-7) is an important biomarker recently investigated in this regard [5–7]. It is secreted from damaged renal tubular cells and is responsible for inhibiting endothelial proliferation through kinase activation, cell aging pathway, and tumor suppression [5]. [TIMP-2] × [IGFBP7] has FDA approval for clinical risk assessment and nephrotoxicity in acute kidney injury [5]. Therefore, it can be used for clinical risk assessment for conditions that may develop acute kidney injury. However, there is not enough literature data on IGFBP 7. We planned to investigate the efficacy of IGFBP 7 in assessing clinical risk and predicting nephrotoxicity in
acute kidney injury. For this reason, we planned this study to evaluate its effectiveness in the prediction of diuretic-induced acute kidney injury.

In this study, we examined serum IGFBP7 levels before and during the treatment of patients with stage-III and stage-IV heart failure (HF) who had no kidney diseases in medical history and were treated with loop diuretic (furosemide). In this study, we aimed to investigate whether the cut-off levels of IGFBP7 and the changes in its level that may occur with treatment. The study can provide information about iatrogenic renal failure that may concomitantly occur with heart failure treatment.

**Methods**

This is a prospective observational study conducted in a tertiary emergency department. The study was approved by the University Clinical Research Ethics Committee, decision no 2019/17-14 (KA-180079). Approval was also received from the Ministry of Health, Pharmaceuticals and Medical Devices Agency, Department of Clinical Research (decision number: 66175679-516.04.01-E.171613).

The patients, who admitted to the ED with shortness of breath, swelling in the body, chest pain, decreased urine output and had undergone subsequent examinations and treatment with a preliminary diagnosis of stage III – IV heart failure, were included in the study. Patients who were not treated in accordance with the stage III – IV heart failure treatment protocol defined in international guidelines were excluded from the study. Exclusion criteria were having a kidney disease, receiving intravenous radiopaque contrast in the past 3 weeks, being in sepsis or septic shock, refusing to participate in the study and having renal transplantation.

Written informed consents were obtained from all patients. Blood samples were collected from the patients for analysis at the admission.

In line with the recommendations of the International Cardiology guidelines, the patients’ blood pressure —i.e., mean arterial pressure of >65 mm Hg—and the suitability of vital signs and laboratory parameters —such as creatinine levels and a glomerular filtration rate of >60 mL/min—were evaluated. The patients who met these criteria received the following predetermined treatment protocol we routinely use in our center: a total of 80 mg furosemide in divided doses consisting of 40 mg intravenous push and 40 mg/2 h intravenous (IV) infusion.

The half-life of the furosemide used in the treatment was 4–6 h. Considering the half-time of the drug and the follow-up period in the ED, blood samples were collected from the patients three times, i.e., at the baseline (0), at 6h and at 12h hour after treatment initiation. This has ensured so that at least two half-lives have passed.

Serum was extracted from the collected blood samples via centrifugation at 4,000 rpm for 5 min. IGFBP7, creatinine and GFR analyzes were performed in the obtained serum samples.

**IGFBP 7 measurement**

Blood samples were collected into serum separator tubes, centrifuged for 10 min at 1,000xg, then stored in aliquots at ~80 °C for later use. IGFBP7 levels in serum samples were measured by ELISA kit (Cloud-Clone Corp). Before analyzes, serum samples were diluted 100-fold by 0.01 mol/L PBS (pH=7.2). The concentration of IGFBP7 in the samples was measured spectrophotometrically at 650 nm, then determined by using the standard curve. The concentrations of the standards were 10, 5, 2.5, 1.25, 0.625, 0.312, 0.156 ng/mL. Detection rate of the method was 0.156–10 ng/mL, intra-assay CV was <10% whereas inter-assay CV was <12%.

**Creatinine measurement**

Creatinine was measured by modified kinetic Jaffe procedure on AU680 analyzer (Beckman Coulter, USA), in which creatinine reacts with picric acid at alkaline pH to form a yellow-orange complex. The rate of change in absorbance at 520/800 nm is proportional to the creatinine concentration in the sample. The within run precision for serum samples is less than 3% CV and total precision is less than 6% CV. The method is linear from 0.2 up to 25 mg/dL for serum samples.

**GFR measurement**

CKD-EPI equation is used for estimating GFR:

\[
\text{GFR} = 141 \times \min(\text{Scr}/\kappa, 1) \times \max(\text{Scr}/\kappa, 1) - 1.209 \times 0.993^{\text{Age}} \\
\times 1.018[\text{if female}] \times 1.159[\text{if black}]
\]

All patients were followed up at least 12 h. The baseline creatinine and GFR levels of the patients were compared with 12h hour levels. Changes in 0, 6h, and 12h hour GFR and creatinine values were evaluated with RIFLE criteria. Variations between these results were classified according to the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) criteria (Table 1).

Patients who did not have a medical history of kidney disease and had stage III – IV heart failure were included in the study. A total of 84 patients were included in the study, and all patients received IV diuretic therapy in accordance with a predetermined protocol. Blood samples were collected to evaluate IGFBP7 and creatinine levels before the treatment (baseline = 0 h) and at 6h, and 12h hour after the first treatment. As the primary endpoint, the creatinine level and glomerular filtration rate (GFR) of the patients at baseline were compared with the 12h hour values. The results were classified according to the RIFLE. The patients were divided into two groups as those in any RIFLE group (RIFLE +) and those without (RIFLE −). The groups were compared in terms of IGFBP7 levels.

| Category | Serum creatinine or GFR |
|----------|-------------------------|
| Risk     | Increase in serum creatinine by 1.5 times or decrease in GFR by >25% |
| Damage   | Increase in serum creatinine by 2 times or decrease in GFR by >50% |
| Failure  | Increase in creatinine level by 3 times or serum creatinine of >4 mg/dL (>354 μmol/L) acute rise of >0.5 mg/dL (>44 μmol/L) or decrease in GFR by >75% |
| Loss of function | Persistent acute renal failure or complete loss of kidney function for >4 weeks |
| End-stage renal disease | >3 months |

**Table 1: RIFLE classification system.**
Statistical analysis

The data obtained from the study were analyzed with the Statistical Package for the Social Sciences 23 program. Quantitative variables were expressed in mean, standard deviation and median, and qualitative variables were given in number of observations and relative frequency (%). Chi-square analysis was used to determine whether there was a significant relationship between qualitative variables and RIFLE (+) and RIFLE (−) groups. Kolmogorov–Smirnov and Shapiro–Wilks tests were used to investigate whether the quantitative variables showed normal distribution.

In comparisons under the RIFLE classification, independent two-sample t-test was used for those with normal distribution, and non-parametric Mann–Whitney U test for those non-normally distributed. Analysis of variance in repeated measurements was used to check whether there was a difference between time-dependent evaluations. In cases where the assumption of normality was not met, the Friedman test was used. With ROC analysis, the discriminative power of the test and the appropriate positivity threshold were determined, sensitivity and specificity were defined. The results were analyzed at 95% confidence interval, and p<0.05 indicated statistical significance.

Results

The flowchart of study is shown in Figure 1. The demographic characteristics of the patients in the study are given in Table 2.

There is a statistically significant difference between RIFLE (+) and RIFLE (−) groups in terms of IGFBP7 levels at 0, 6th, and 12th hour (p=0.036, 0.042, and 0.006, respectively). In all three measurements, IGFBP7 values were found to be higher in RIFLE (+) group than RIFLE (−) group.

For IGFBP7 measurements, the cut-off with the highest sum of sensitivity and selectivity is 118.71 ng/mL. When this point was considered as the optimal cut-off, the specificity and sensitivity was 69 and 80%, respectively.

The value of the area under the ROC curve is 71.4%. The 95% confidence interval for this area was 58.2 and 84.5%. The result obtained is statistically significant (p=0.006) (Figure 2).

Table 2: Demographic characteristics.

| Variable  | RIFLE (+) | RIFLE (−) | p-Value |
|-----------|-----------|-----------|---------|
| Gender    | Male (%)  | Female (%)|         |
| n         | 11 (50%)  | 30 (48.4%)| 0.473   |
| Age, year | 74.7 ± 10.1| 72.2 ± 9.8| 0.913   |
| Standard deviation |          |          |        |
| Initial creatinine (mean), mg/dL | 0.89 ± 0.19 | 0.83 ± 0.22 | 0.335 |
| Mean glomerular filtration rate, mL/min/1.73 m² | 59.4 | 58.06 | 0.329 |
| Creatinine at 12 h (mean), mg/dL | 1.17 ± 0.21 | 0.81 ± 0.28 | <0.001 |

Table 3: Comparison of IGFBP7 in subjects with and without kidney damage according to RIFLE.

| Variable | Time, h | RIFLE (+) | RIFLE (−) | p-Value |
|----------|---------|-----------|-----------|---------|
| IGFBP7   | 0       | 116.84    | 167.87    | 0.036   |
|          | 6       | 114.82    | 158.60    | 0.042   |
|          | 12      | 103.54    | 181.13    | 0.006   |
| p        |         | 0.360b    | 0.116b    |         |

aMann–Whitney U test. bFriedman test.

Figure 1: Flowchart of the study.

Figure 2: Receiver operating characteristic (ROC) analysis for IGFBP7 in the RIFLE (+) group (AUC: 71.4%. 95% CI: 58.2–84.5%).
Discussion

Serum creatinine is frequently used to diagnose AKI but considered as an insensitive and delayed diagnostic biomarker [8]. Unlike the serum creatinine value, IGFBP 7 has been shown to be a biomarker that can diagnose AKI at an earlier stage [9]. The levels of these biomarkers can be measured separately in urine and serum. For a similar purpose, tests of bedside IGFBP7 with dipstick method have also been used for rapid analysis in urine [10]. In the present study, we evaluated IGFBP7 levels in serum using the ELISA test. Measuring IGFBP7 with the ELISA method is a quantitative procedure with higher sensitivity and specificity. There are some limitations of the evaluations made with the urine IGFBP7 levels [11]. Bai et al. showed that no significant difference was found between serum and urine IGFBP 7 levels in terms of predicting acute kidney injury [12].

According to the literature, the timeframe in which changes in IGFBP7 could be detected was 12–36 h [13]. Kashani et al. identified the primary endpoint in their study as detecting AKI developing after 12 h [7]. Schanz et al. investigated the predictive ability of urinary [TIMP-2]×[IGFBP7] levels for development of AKI in patients with acute decompensated heart failure in ED [14]. The samples were collected at 0, 6th, 12th hours, and daily thereafter for 7 days. In a study by Bai et al. in which samples were analyzed for IGFBP7 measurements to detect AKI in children hospitalized in the intensive care unit (ICU), samples were collected only within 24 h of admission to the ICU [12]. For this reason, the evaluations in our study were made with serum IGFBP7 levels. After evaluating previous studies, it was decided to evaluate the results of serum IGFBP7 levels at 0, 6th and 12th hours.

Bai et al. studied IGFBP7 in both blood and urine samples for early detection of kidney damage in pediatric patients followed in the ICU [12]. They found the cut-off value in serum for severe AKI condition as 125.26 ng/mL. In our study, in the ROC analysis performed to determine the cut-off for the IGFBP7 level, the cut-off with the highest sum of sensitivity and specificity was found to be 118.71 ng/mL (sensitivity 80% and specificity 69%). The ROC analysis for the cut-off for the IGFBP7 level in our study was similar to previous studies in literature.

Bai et al. found that increased urinary IGFBP7 predicted AKI in children hospitalized in the ICU, regardless of the severity of the disease [12]. Our results are in line with the literature. A statistically significant difference was found between RIFLE (+) and RIFLE (−) patients in terms of IGFBP7 measurements at baseline, 6th, and 12th hours. It was determined that the IGFBP7 value was higher in RIFLE (+) subjects than in RIFLE (−) subjects at all 3 h. In both RIFLE (+) and RIFLE (−) patients, IGFBP7 measurements did not change over time. These values did not increase depending on the degree of damage. We found similar results with the literature in that AKI developed in patients with high IGFBP7 levels, but these values did not increase depending on the degree of damage.

In our study, no time-dependent changes were detected in serum IGFBP7 levels at 0, 6, and 12 h. There was no significant increase in IGFBP 7 values measured for the RIFLE (+) and RIFLE (−) groups compared to baseline (p=0.360/p=0.116). However, for each measurement time (0, 6th, and 12th hours), IGFBP 7 levels measured in the RIFLE (+) group differed significantly from the RIFLE (−) group (values and p). In the light of this information, we can suggest that measuring IGFBP7 levels, before furosemide therapy in acute decompensated heart failure patients, could play an important role in predicting the likelihood of development of AKI.

This study has some limitations. Since it is a study conducted in a single center, the results obtained may not be generalizable to the entire population. The sample size for this study is small. Multicenter studies with larger sample size are needed to determine the importance of IGFBP7 7 better in acute renal injury.

Conclusions

The results of this study suggest that measuring IGFBP7 levels before starting the treatment in patients with stage III–IV heart failure can help predict the risk of developing AKI and plan preventive treatment for AKI. Early measurements of IGFBP7 levels were recommended to predict diuretic-induced acute kidney injury in congestive heart failure. But multicenter studies including larger subjects should be planned to prove the predictive value of IGFBP7 in acute kidney injury.

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