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Akut Böbrek Hasarında uMMP7 ile Prognoz, Komorbidite ve Mortalite Arasındaki İlişki

Relationship Between uMMP7 and Prognosis, Comorbidity and Mortality in Acute Kidney Injury

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ÖZ

Giriş: uMMP7 son yıllarda çok çeşitli hastalıklarla ilişkilendirilen bir moleküldür. Bu çalışmadaki amacımız akut böbrek hasarı (ABH) nedeniyle kliniğimizde yatan hastalarda uMMP7'nin komorbid durumlar, mortalite ve kısa dönem ABH prognozu ile ilişkisini incelemektir.

Yöntem: Kliniğimizde ABH tanısıyla takip edilen 160 hasta çalışmaya dahil edildi. Yaş, cinsiyet, başvuru anındaki kreatinin düzeyi, bazal kreatinin düzeyi, taburculuk sonrası kreatinin düzeyi, başlangıç glomerüler filtrasyon hızı (GFR), bazal GFR, kontrol GFR, komorbiditeler, kalıcı renal replasman tedavisine (RRT) geçiş, mortalite ve Hastaların uMMP7 düzeylerine bakıldı.

Bulgular: Komorbid hastalıklardan uMMP7 düzeyi sadece hipertansiyon hastalarında anlamlı olarak düşük bulundu (p=0,001). Bu durum anjiyotensin dönüştürücü enzim inhibitörü (ACEI) kullanımı ile ilişkiliydi. Başvuru anındaki UMMP-7 düzeyi ile kreatinin düzeyi arasında anlamlı ve pozitif bir ilişki, başvuru anındaki GFR düzeyi ile ise istatistiksel olarak anlamlı ve negatif ilişki bulunmuştur. AKIN kriterine göre evre 3 hastaların idrar MMP7 düzeyi, evre 1 ve evre 2 olanlara göre anlamlı derecede yüksekti(p=0,004). RIFLE kriterine göre 3. derece hastaların uMMP7 düzeyi 2. derece hastalara göre anlamlı olarak yüksek bulunmuştur.

Sonuç: ABH'nin şiddeti arttıkça uMMP7 düzeyi de artmaktadır. Hipertansiyon hastalarında uMMP7 düzeyi anlamlı derecede düşüktü ve bu durum ACEI kullanımıyla ilişkiliydi.

Anahtar Kelimeler: ABH, hipertansiyon, morbidite, uMMP7

ABSTRACT

Objective: uMMP7 is a molecule that has been associated with a wide range of diseases in recent years. Our aim in this study is to examine the relationship of uMMP7 with comorbid conditions, short-term mortality and acute kidney injury (AKI) prognosis in patients hospitalized in our clinic due to AKI.

Method: 160 patients who were followed up in our clinic with the diagnosis of AKI were included in the study. The relationship among age, gender, creatinine level at admission, basal creatinine level, post-discharge creatinine level, initial glomerular filtration rate (GFR), basal GFR, control GFR, comorbidities, transition to permanent renal replacement therapy (RRT), mortality and uMMP7 levels of the patients were examined.

Results: Of the comorbid diseases, the uMMP7 level was found to be significantly lower only in hypertension patients(p=.001).This was associated with the use of angiotensin converting enzyme inhibitor (ACEI). A significant and positive relationship was found between the uMMP7 level and the creatinine level at admission, and a statistically significant and negative relationship was found with the GFR level at admission. According to the AKIN criteria, the uMMP7 level of Grade 3 patients was significantly higher than those who are grade 1 or grade 2(p=.004). According to the RIFLE criterion, the uMMP7 level of grade 3 patients was found to be significantly higher compared to the grade 2 patients.

Conclusion: As the severity of AKI increases, uMMP7 level increases. uMMP7 level was significantly lower in hypertension patients, and this was associated with the use of ACEI.

Keywords: AKI, hypertension, morbidity, uMMP7

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INTRODUCTION

MMPs, also known as matricines, are a group of calcium-dependent endopeptidases whose active site is zinc, which lead to reshaping by breaking down proteins in the extracellular matrix (ECM). (1). MMP7 belongs to the matrix subgroup of metalloproteinases (2). The activities of MMPs are restricted by two types of endogenous inhibitors. The first of these is specific endogenous tissue inhibitors (TIMP) (3).It provides inhibition by combining with MMPs and closing the catalytic area and hemopexin areas (4). Four TIMPs (TIMP-1–4) were identified in vertebrates and have structures compatible with the active region of the catalytic area of the MMPs. TIMP1 and TIMP2 have been shown to act as growth factors in some cancers (1). Another inhibitor of MMPs is alpha 2 macroglobulin (5). Metalloproteinases involved in ECM reshaping are involved in such as pregnancy, wound healing, angiogenesis, embryonic development, hair follicle cycle, bone reshaping, cervical dilatation, apoptosis, endometrial cycle, ovulation, while they are also responsible for pathological tissue destruction such as atherosclerosis, aneurysm, myocardial infarction, arthritis, ulcer, emphysm, nephritis, encephalomyelitis, tumor invasion, and metastasis (6).

MMP 7 was first discovered in the womb of the rat (7, 8). It is synthesized by epithelial cells, fibroblasts, keratinocytes, macrophages, especially liver, salivary glands, pancreas, reproductive organs, and glandular epithelial cells of the breast (9). MMP-7 also plays an important role in natural immunity by activating antimicrobial peptides such as pro-defensin and stimulating the release of TNF from macrophages (10). The transcription of MMP-7 is regulated by Wnt/β-catenin and TGF-β (11). The ECM plays an important role in the stabilization of atherosclerotic cap. MMP-7 plays an important role in deterioration of the plaques and tissue on the arterial wall (12). MMP-7 is synthesized in the renal tubular epitheliumis and excreted in urine(13). In some studies, it was observed that MMP-7 activity increased in a wide range of renal diseases (7, 14). When MMP inhibition was performed before the proteinuria stage, kidney damage regressed, while MMP inhibition advanced the damage after the proteinuria stage started(15).

Renal fibrosis is a pathological consequence of CKD caused by excessive ECM accumulation (16) . Activation of wnt/β-catenin in the kidney is known to be associated with fibrosis (17). It has also been proven that wnt/β-catenin activation increases uMMP7 transcription. It is possible to measure uMMP7 level as another option for evaluating renal fibrosis (14). It was observed that urine MMP9 level increased as proteinuria increased in patients with diabetic nephropathy (DNP) (18). In type 1 diabetes mellitus (DM), an increase in urinary MMP7 excretion was detected and showed positive correlation with high glycemic values and albuminuria (19). In a study published, MMP7 expression was examined in various AKI models and the role of MMP7 in AKI was tried to be understood using mice whose MMP7 gene was deactivated.In models where the MMP7 gene was deactivated, a greater increase in NGAL, a higher creatinine increase, and more serious morphological damage were observed. Based on the fact that morphological changes such as higher mortality rate, tubular cell loss and brush border deletion were more severe in those without the MMP7 gene by 72% to 20%, MMP7 loss has been shown to exacerbate cisplatin-induced AKI. In order to better explain the importance of MMP7 in AKI, MMP-7 negative mice were injected with exogenous MMP7 and it was observed that renal functions were largely preserved. (20).

This study aims to examine the relationship between uMMP7 level and morbidity, comorbidities and mortality in patients hospitalized for AKI.

MATERIALS AND METHODS

This prospective study evaluated volunteers who were admitted to the Nephrology Clinic with the diagnosis of AKI. Approval was received from the local ethics committee of Selcuk University Faculty of Medicine (approval number 2020/543)The patients were selected from those who volunteered to participate in the study and a written informed consent form was obtained. Information such as age, gender, comorbid diseases, used drugs regarding the 160 patients diagnosed with AKI, who were eligible for the study, was questioned, and urine samples were collected during routine examinations. Patients' creatinine level at admission, basal creatinine level, control creatinine level, first GFR, basal GFR, GFR at the time of control, status of RRT, mortality status were evaluated. Serum creatinine levels were used for the diagnosis of AKI. The patients were grouped according to RIFLE and AKIN stages. Urine samples were placed in 10 ml tubes and stored at -80°C. Among these stored samples, the uMMP7 level was studied by ELISA (Enzyme-Linked Immunosorbent assay) method as indicated in the catalog of the manufacturer (Human TOTAL MMP7 Quantikine Elisa Kit). For AKI, the highest creatinine level at admission and the lowest GFR value were taken as creatinine levels. For the prognosis determination, control creatinine values were examined 59 days after the first recorded creatinine of the patients. Patients with a procalcitonin value greater than 0.5 ug/L at admission were included for sepsis status (21).

Statistical Analysis

All statistical analyzis were performed by Selçuk University Faculty of Medicine Department of Biostatistics using the program R version 3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). Before the analyses, the normality of the data was checked by the Shapiro-Wilk normality test and Q-Q graphs, and the homogeneity of the group variances was checked by the Levene test. Descriptive statistics for numerical variables were submitted as average ± standard deviation or median (IQR: interquartile range) or as frequency (n and percentage (%)) for categorical variables. The effect of urinary MMP7 level on prognosis and its relationship with other diseases in patients with acute renal failure and without chronic renal failure were examined with the Mann-Whitney U test, and its relationship with creatinine and GFR was examined with Spearman's rho correlation coefficient. The differences of uMMP7 level according to the AKIN and RIFLE criteria were examined by the Kruskal Wallis test, and the paired comparisons for the variables with significant difference were examined by the Bonferroni-corrected Dunn test. The significance level was taken as 5%.

RESULTS

There were 160 patients in total, the age range was 19-94 years (67.95 ± 16.04) and 50.6% of the patients were male. The overall mortality rate was found to be 15.6%. The effect of uMMP7 level on the prognosis of AKI is presented in the Table 1.

Table 1. The Effect of MMP-7 Level on Prognosis in AKI

		n	Urinary MMP-7 level (ng/ml)	*p*-value
Partial recovery	unrecovering	61	12.39 (9.10 – 14.73)	.309
	recovering	86	12.02 (6.38 – 14.55)	
Complete recovery	unrecovering	90	12.09 (8.99 – 14.70)	.337
	recovering	57	12.22 (6.22 – 14.54)	
Exitus	Living	122	12.18 (7.97 – 14.56)	.817
	Death	25	12.26 (7.36 – 14.70)	

Data are presented as median (IQR: interquartile range). The p-value was calculated with the Mann-Whitney U test.

It was found that there was no statistically significant relationship between uMMP7 level and prognostic factors(p> .05). The relationship between uMMP7 level and other diseases was examined in the Table 2.

It was determined that the uMMP7 level was significantly lower only in hypertensive patients (11.15 [IQR, 6.93 – 14.21] vs. 14.34 [IQR, 12.26 – 15.06], p= .001). The uMMP7 level in patients using ACEI or ARB (9.45 ± 4.88 ng/ml) was significantly lower (11.6 ± 4.42 ng/ml) (p=0.003) (Table 3). When we split the patients as those who use ACEI and non-users, uMMP7 levels were significantly lower in ACEI users (8.79 ± 5.29 ng/ml) compared to the non-users (11.10 ± 4.60 ng/ml) (p=0.05)

The relationship between MMP7 level and creatinine and GFR is shown in Table 4.

A significant and positive correlation was found between uMMP7 level and creatinine level at the time of admission (Spearman's rho=0.361, p< .001), and a statistically significant and negative correlation was found between uMMP7 and GFR level at the time of admission (Spearman's rho=-0.352, p< .001) (Figure 1).

The relationship between uMMP7 level and AKIN and RIFLE criteria was examined in the Table 5.

The uMMP7 level of the patients determined as Grade 3 (14.09 [IQR, 10.10 – 14.97] according to the AKIN criterion was significantly higher than those determined as Grade 1(10.52 [IQR8.39 – 13.94], Bonferroni p = .040) and Grade 2 (10.19 [IQR, 5.60 – 12.57], Bonferroni p = .010) (p= .004). The uMMP7 level of the patients classified as grade 3 according to the RIFLE criterion was significantly higher compared to the patients classified as grade 2 (14.22 [9.02 – 15.20] vs. 10.14 [6.22 – 14.04], Bonferroni p = .029) (Figure 2).

Diagnostic performance of uMMP7 level in differentiating severe AKI from non-severe AKI. The reference line was colored with light-grey; the ROC curve of uMMP7 level was colored with red (Cut-off value of 12.39 with Sensitivity, 66.7% (95% CI, 55.1 – 76.9); Specificity, 67.1% (95% CI, 55.8 – 77.1); PPV, 65.8% (95% CI, 57.7 – 73.1); NPV, 67.9% (95% CI, 59.9 – 75)) (Figure 3).

Table 2. Relationship Between MMP-7 Levels and Other Diseases

		n	Urinary MMP level (ng/ml)	*p*-value
Sepsis	No	107	11.91 (7.85 – 14.41)	.192
	Yes	53	13.69 (8.92 – 14.89)	
DM	No	97	12.75 (7.81 – 14.70)	.711
	Yes	63	12.22 (8.82 – 14.50)	
Hypertansion	No	49	14.34 (12.26 – 15.06)	.001
	Yes	111	11.15 (6.93 – 14.21)	
Cardiovascular disease	No	107	13.06 (8 – 14.65)	.451
	Yes	53	11.56 (7.75 – 14.42)	
Rheumatological disease	No	144	12.18 (7.66 – 14.54)	.135
	Yes	16	14.43 (9.59 – 14.96)	
Neurological disease	No	139	12.26 (8 – 14.58)	.998
	Yes	21	13.06 (6.38 – 14.83)	
Malignancy	No	139	12.13 (7.88 – 14.53)	.266
	Yes	21	14.22 (8.92 – 14.70)	
Renal transplantation	No	156	12.37 (7.91 – 14.61)	.952
	Yes	4	10.79 (7.98 – 14.18)	
Thyroid diseases	No	154	12.37 (7.97 – 14.59)	.833
	Yes	6	10.88 (6.58 – 14.50)	
End-stage renal disease	No	136	12.39 (8 – 14.57)	.863
	Yes	24	11.91 (6.95 – 14.73)	
Hepatic cirrhosis	No	156	12.41 (8.03 – 14.65)	.201
	Yes	4	8.37 (6.21 – 10.27)	

Data are presented as median (IQR: interquartile range). The p-value was calculated with the Mann-Whitney U test.

Table 3. Relationship Between ACEI or ARB use and u-MMP7 Level				
		ACEI or ARB		
		No	Yes	
Hypertension	No	14.28 (11.78 – 15.04)	15.19 (15.19 – 15.19)	.377
	Yes	11.96 (8.96 – 14.66)	10.52 (5.88 – 13.55)	.061
	All patients	**13.75 (9.18 – 14.77)**	**10.56 (6.05 – 13.77)**	**.003**
ACEI angiotensin converting enzyme inhibitors, ARB angiotensin receptor blockers				

Table 4. u-MMP7 Levels by ACEI or ARB use		
	Urinary MMP-7 Level (ng/ml)	p-value
ACEI or ARB users (n=60)(n=60) Not using ACEIs or ARBs (n=100)	9,45 ± 4,88 11,6 ± 4,42	**0,003**
ACEI users (n=17) Not using ACEI (n=143)	8,79 ± 5,29 11,10 ± 4,60	**0,05**
ARB users (n=46) Not using ARB (n=114)	9,92 ± 4,71 11,2 ± 4,68	0,11
ACEI angiotensin converting enzyme inhibitors, ARB angiotensin receptor blockers		

Table 5. Relationship Between µMMP-7 Level, Creatinine and GFR		
	Urinary MMP-7 level (ng/ml)	
	Spearman'ın *rho*	*p*-value
Creatinine level at admission (mg/dl)	0.361	<.001
Basal creatinine level (mg/dl)	0.071	.390
Control creatinine level (mg/dl)	0.143	.084
Number of days between hospitalization and control creatinine	–0.021	.799
GFR level at admission (ml/min/1.73m2)	–0.352	**<.001**
Control GFR level (ml/min/1.73m2)	–0.139	.094
Basal GFR level (ml/min/1.73m2)	–0.035	.673

Table 6. Relationship Between MMP-7 Level and AKIN and RIFLE Criteria				
		n	**Urinary MMP-7 level (ng/ml)**	***p*-value**
AKIN criteria	Grade 1	55	10.52 (8.39 – 13.94)[a]	.004
	Grade 2	27	10.19 (5.60 – 12.57)[a]	
	Grade 3	78	14.09 (10.10 – 14.97)[b]	
RIFLE criteria	Grade 1	37	10.85 (8.73 – 13.81)	.015
	Grade 2	45	10.14 (6.22 – 14.04)[a]	
	Grade 3	63	14.22 (9.02 – 15.20)[b]	
	Grade 5	15	13.90 (12.16 – 14.57)	
Data are presented as median (IQR: interquartile range).The p-value was calculated with the Kruskal Wallis test, followed by multiple comparisons using the Bonferroni-corrected Dunn test. Different superscripts in columns indicate statistically significant difference.				

DISCUSSION

uMMP7 expression is almost absent in normal kidney. Its expression is induced in AKI (22, 23). It exerts a protective effect against AKI (10). There is increasing evidence and studies that uMMP7 is a noninvasive marker for predicting AKI prognosis and monitoring CKD progression (13, 24). There is increasing evidence and studies that uMMP7 is a noninvasive marker for predicting AKI prognosis and monitoring CKD progression (13, 24). In a study conducted by Afkarian et al., uMMP7 concentration was associated with increased mortality in proteinuric diabetic kidney disease patients (25). In contrast, in a study conducted by Agarwal et al. for 24 biomarkers including uMMP7 in 67 US veterans with diabetic kidney disease, no correlation was found between uMMP7 level and ESRD or mortality. We did not find any association between uMMP7 level and mortality or ESRD in AKI (26). Yang et al. investigated whether uMMP7 level could be a biomarker that could be used to predict progression in 946 patients with biopsy-proven IgAN. Risk assessment of IgA nephropathy progression was performed on seven other markers. Among these markers, uMMP7 had the strongest association with IgA progression (27). We found that there was no statistically significant association between uMMP7 level, one of the prognostic factors, and complete recovery and exitus. The possible reason may be that our study group consisted of patients with AKI of very diverse etiologies.

In another study, uMMP7 was compared with five biomarkers to predict the severity of AKI after cardiac surgery. uMMP7 levels were significantly higher in both adults and children who developed severe AKI (KDIGO stage 2 or 3). No significant change was found in plasma MMP7 levels in all patients with or without AKI. In this study, increased uMMP7 levels predicted AKI, and higher uMMP7 levels were associated with severe AKI (13). In our study, we found that uMMP7 levels increased as AKI severity increased. What induces MMP7 activity in the damaged kidney is still a subject of investigation. Some studies have shown that it is associated with canonical Wnt/β-catenin activity (14). In a study by Surendran et al., folic acid nephropathy was identified as a model of AKI for matrixilin mRNA expression in mice. MMP7 expression was induced in all animals and the degree of MM7 mRNA induction was associated with renal dysfunction(28). In our study, we found a significant and positive correlation between u-MMP7 level and creatinine level and a negative correlation with GFR level.

Among comorbid diseases, we found that uMMP7 levels were significantly lower in hypertensive patients. Subgroup analysis showed that this difference persisted in ACEI users and was related to ACEI use. Zervoudaki et al. measured plasma concentrations of active MMP2 and MMP9 in untreated essential hypertensive and normotensive individuals. MMP2 and MMP9 were found to be suppressed in essential hypertensive patients (29). Li-Saw-Hee FL et al. also found that both MMP9 and TIMP-1 were significantly lower in untreated hypertensive patients compared to normotensive controls (30). Angiotensin II induces the synthesis of plasminogen activator inhibitor-1 (PAI-1). PAI-1 inhibits plasmin-mediated activation of MMP. ACEI has been shown to inhibit MMP in many studies (31, 32). Hotchi and colleagues demonstrated the plaque-stabilizing effects of ACEI and ARBs. Furthermore, ACEI was shown to reduce MMP9 expression and gelatinolytic activity in the intima, while ARB did not alter gelatinolytic activity (33). Wang and colleagues showed that MMP7 expression was reduced only in the ACEI group in mice with implanted gastric cancer (34). Inhibition of the renin-angiotensin system by ACEI and ARB has been shown to treat hypertension and proteinuria (35). In addition to its hemodynamic effects, angiotensin II has several other effects on glomerular cells, such as induction of cytokine production. Angiotensin II stimulates mesangial cell proliferation and induces TGF-β expression (36). Lods et al. found that MMP activities in patients with biopsy-proven glomerular inflammatory disease were similar in patients with untreated glomerulonephritis and in patients treated with ARBs, whereas MMP activity was reduced in patients treated with ACEIs (32). Martinez Fierro et al. showed that urinary MMP2 concentration increases the risk of developing PE in women (37). In our study, the lower uMMP7 level in the ACEI-only group is consistent with these studies.

The limitations of this study are that it is a single-center study, the follow-up period is relatively short, and the etiologies of AKI in the patients are heterogeneous.

CONCLUSION

In accordance with the literature, uMMP7 level increases as the severity of AKI increases. We can say that it is a marker showing the severity of AKI but we could not determine its relationship with prognosis. We also found that uMMP7 levels are significantly lower in hypertensive patients associated with the use of ACEI.

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Author Contributions: FB(writing, data collection, data entry), YCY (data collection, review), ZB(data entry), MKKorez(statistical analysis), SA(biochemical analysis), Lutfullah A(review)

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