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Association between Kidney Injury Molecule-1 Gene Polymorphism and Acute Kidney Injury among the Lebanese Patients

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Abstract

Acute kidney injury is a common condition associated with longer hospital stay and increased mortality. Kidney injury molecule-1 (*KIM-1*) is one of the early and sensitive biomarkers for acute kidney injury diagnosis. Therefore we examined the relationship between kidney injury molecule-1 gene polymorphism and acute kidney injury in Lebanese hospitalized patients. Genomic DNA was isolated from blood samples collected from 50 patients and 40 controls. Kidney injury molecule-1 exon 4 was amplified by polymerase chain reaction and the amplified products were sequenced at MacroGen. Serum creatinine and urea levels were measured and compared between controls and patients. Three out of the five known single nucleotide polymorphisms showed significant association with susceptibility to the disease ($P \leq 0.05$). Data analysis implied that carriers of the risk allele of these 3 single nucleotide polymorphisms were more predisposed to acute kidney injury. No association was found between the studied nucleotides variations and creatinine/urea levels. Haplotype analysis showed high association of the block CTA with acute kidney injury incidence and high creatinine and urea levels. Our results suggest that polymorphisms in exon 4 of kidney injury molecule-1 in the Lebanese population may be associated with acute kidney injury.

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Introduction

Acute kidney injury (AKI) is one of the serious kidney conditions that is associated with increased mortality rate (Uchino et al., 2005). The variability in the prediction of adverse kidney-related outcomes still has no significant explanation. In recent years, the role of genetic single nucleotide polymorphisms

as possible determinants of adverse outcomes in AKI patients and the severity of the disease has been the interest of many studies (He et al., 2018; Leung et al., 2009; Susantitaphong et al., 2013).

Due to known limitations in creatinine and urine output tests, the “gold standard” of AKI biomarkers,

new specific, early, and more sensitive biomarkers are needed. Recently, kidney injury molecule-1 (KIM-1) is being considered as a promising biomarker for AKI and kidney failure (Martensson, Martling, & Bell, 2012). *KIM-1*, also known as T cell immunoglobulin and mucin-1 (TIM-1) or hepatitis A virus cellular receptor 1 (HAVCR1), is a type I transmembrane glycoprotein expressed by the proximal tubular epithelial cells (Vaidya, Ferguson, & Bonventre, 2008). The precise role of KIM-1 in renal injury and repair and whether its expression enhances renal protection from nephrotoxic insult is not well established. KIM-1 was shown to play an important role in signaling phagocytosis of apoptotic cells by renal proximal tubular epithelial cells, thus promoting tissue remodeling, restoring tissue normal integrity, and facilitating repair (Rees & Kain, 2008). This molecule was also demonstrated as an early sensitive and specific diagnostic marker for kidney injury in humans and rats exposed to toxic substances (Vaidya et al., 2006).

Genetic polymorphisms of *KIM-1* have major effects on its function in the immune system and thus susceptibility to immune diseases (Meyers et al., 2005). It is important to clarify whether these polymorphisms affect the susceptibility to AKI or to progressive renal injury, and thus may lead to novel therapeutic strategies. Therefore, the aim of this study is to examine the relationship between *KIM-1* gene polymorphism and acute kidney injury in Lebanese hospitalized patients.

Material and methods

Study Population and Data collection

A total of fifty AKI patients (28 male and 22 females), age range between 18 and 90 years (mean 56.86 ± 20.4 years) were recruited from several hospitals in North Lebanon and from Beqaa between November 2017 and May 2018. Forty non-AKI controls with healthy kidneys (21 male and 19 females) ranging between 19 and 88 years old with mean age of 53 ± 20.3 were recruited from the same regions.

Detailed clinical history records were collected. Kidney-related parameters including serum

creatinine and blood urea nitrogen (BUN) were retrieved from hospitals' records.

Patients with AKI were recruited with the help of nephrologists from the hospitals: Tripoli Governmental Hospital (Nephrology and Dialysis department), Orange Nassau Governmental Hospital (Nephrology and Dialysis department), and Bekaa Hospital (Nephrology and Dialysis department). Patients were selected according to the Kidney Disease criteria: Improving Global Outcomes (KDIGO) criteria. AKI patients were defined as patients with at least 1.5-1.9 times or ≥ 0.3 mg/dl increase in serum creatinine from baseline within 48 hours (Kellum, Lameire, & Group, 2013).

Exclusion criteria included participants younger than 18 years, patients undergoing chronic dialysis therapy, pregnant women, and non-Lebanese participants.

The study was approved by the "Institutional Review Board" at Beirut Arab University. Informed consent was obtained from all individual participants included in the study, and a well-designed questionnaire that included baseline demographic characteristics, as well as comorbidity and coexisting conditions was filled.

DNA extraction and PCR amplification

Blood was collected in EDTA tubes from patients and controls during medical visit. Genomic DNA was extracted using the GenElute extracted kit (Sigma-Aldrich, country of origin) according to manufacturer's recommendation. DNA integrity was confirmed by agarose gel electrophoresis while concentrations and purity were determined by spectrophotometric measurement (Evolution 60S UV-Visible Spectrophotometer, Thermo Scientific).

The sequence of primers used to amplify exon 4 of *KIM-1* gene were obtained from Page et al. (Page, Jones, & Stewart, 2006). The sequence of forward primer used was F: 5'-GTTTGACTTATGCTCACTCTC-3' and the reverse primer R: 5'-CCTCACTCTAGACTGTCCTTC-3'.

PCR reaction was performed in a total volume of 25 μ l containing 10 ng template DNA, 0.5 μ l of forward and reverse primers (10 μ M), 12.5 μ l of 2x PCR Master Mixture (Sigma-Aldrich) and 10 μ l of nuclease-free water. PCR was performed in thermocycler (Thermo Electron Corporation Px2

Thermal Cycler, Biocompare) as follows: 1 cycle at 95°C for 3 min, followed by 35 cycles consisting of 30 s at 95°C, 20 s at 50°C and 30 s at 72°C and 1 cycle at 72°C for 4 min. The size of the PCR products obtained was confirmed on 2% agarose electrophoresis and visualized using ChemiDoc-It®2 515 Imager P/N 95-0441-04 UV transilluminator (BIO-RAD, USA). The amplified fragments were purified using GenElute PCR Clean-Up Kit (Sigma-Aldrich, USA) and sent for sequencing at Macrogen, South Korea.

SNP selection

Single nucleotide polymorphisms (SNPs) were chosen for genotyping based on the NCBI SNP database (<http://www.ncbi.nlm.nih.gov>). Five *KIM-1* gene SNPs (rs1401877734, rs781388022, rs1259856748, rs1553316, rs12522248) were selected within exon 4 for genotyping.

Statistical analysis

All statistical analyses were performed using SPSS version 23 program. Chi-square and One-way ANOVA were used to assess SNPs. Odds ratio (OR) and 95% interval confidence (CI) were applied to assess risk factors. P-value of ≤ 0.05 was considered significant.

Results and Discussion

The characteristics of patients and controls are shown in the Table 1. The mean age of participants from both groups of patients and controls were 56.9 ± 20.4 and 53 ± 20.3 years with an average creatinine levels of 3.87 ± 2.15 and 1.01 ± 0.16 mg/dL and with blood urea nitrogen of 140.5 and 23.5 mg/dL, respectively.

Table 1. Characteristics of patients and controls

	AKI patients (n= 50)	Controls (n= 40)
Age ^a	56.9±20.4	53.0±20.3
Gender (male/female)	28/22	21/19
BMI ^a	26.07±4.89	27±5.6
Creatinine ^a (mg/dL)	3.87±2.15	1.01±0.16
Blood urea nitrogen ^a (mg/dL)	140.5±71.17	23.5±2.4

^aValues are shown as mean ±standard deviation

We identified 5 SNPs of *KIM-1* that are associated with susceptibility to acute kidney injury. The genotype frequency and allele frequency of these SNPs selected in exon 4 of *KIM-1* gene in AKI patients and control subjects are shown in Table 2.

As shown, 3 SNPs (rs1401877734, rs781388022, rs1259856748) showed significant differences in the genotypic and allelic frequencies between patients and controls ($P \leq 0.05$). In this study we report the first evidence that genetic variation in *KIM-1* is associated with susceptibility to AKI in Lebanese population. *KIM-1* gene is located on the chromosomal region 5q33.2. It is a member of a family that plays a critical role in regulating immune response and is linked to susceptibility to autoimmune diseases (Garcia-Lozano et al., 2010). Among its 9 exons, exon 4 is known to be highly polymorphic (Lee et al., 2011). *KIM-1* plays an important role in mediating phagocytosis of apoptotic cells within proximal tubule and facilitating recovery from kidney injury by down regulating the immune response (Yang et al., 2015). The first study conducted in 2003 provided evidence for an association between *KIM-1* polymorphism and human atopic disease (McIntire et al., 2003). Gao et al. showed association between *KIM-1* genetic variation and asthma in African American population (Gao et al., 2005). Similarly, Chae et al. showed the association of 10 novel SNPs in the both promoter and coding region of exon 4 of *KIM-1* gene with allergic diseases (asthma and atopic dermatitis) and rheumatoid arthritis in Korean population (Chae et al., 2003). Previous studies identified associations between AKI and other genes. Isbir et al. found the association between angiotensin-converting enzyme (ACE) and apolipoprotein E (APO E) genes polymorphisms and AKI occurrence after cardiac surgery. However, no association was demonstrated between the disease and angiotensin II type 1 receptor (AGTR1) polymorphism (Isbir et al., 2007). Also, no association was found between AKI incidence and catalase, the oxidative stress gene (Perianayagam et al., 2007). Similarly, no significant association was obtained between genes involved in inflammatory and anti-inflammatory pathways and AKI (Stafford-Smith et al., 2005; Treszl et al., 2002).

On the other hand, the association between SNPs in the promoter region of TNF α and IL10 and the decreased death risk in AKI patients was demonstrated (Jaber et al., 2004). Likewise, an association between NFKB Inhibitor alpha gene and

AKI incidence was reported (Bhatraju et al., 2015). In the prior studies, none of the mentioned variations were examined in relation to any disease including AKI, except for rs12522248 and rs1553316. Recently, rs12522248 was found to be

Table 2. Distribution of the genotype and allele frequencies of *KIM-1* gene in AKI patients and controls

	AKI N (%)	Control N (%)	Genotype	P- values	OR (95% CI)
rs1401877734: G>C					
Genotype frequency					
GG	2 (4%)	22 (55%)	(GC+CC) vs. GG	0.000*	Reference Genotype 2.133 (1.507-3.019)
GC	39 (78%)	10 (25%)			
CC	9 (18%)	8 (20%)			
Allele frequency					
Allele G	2 (4%)	28 (70%)	C vs. G	0.000*	Reference Allele 3.200 (1.987-5.155)
Allele C	48 (96%)	12 (30%)			
rs781388022: C>T					
Genotype frequency					
CC	13 (26%)	30 (75%)	(CT+TT) vs. CC	0.000*	Reference Genotype 2.960 (1.689-5.189)
CT	27 (54%)	2 (5%)			
TT	10 (20%)	8 (20%)			
Allele frequency					
Allele C	22 (44%)	32 (80%)	T vs. C	0.001*	Reference Allele 2.800 (1.437-5.454)
Allele T	28 (56%)	8 (20%)			
rs1259856748: C>T					
Genotype frequency					
CC	2 (4%)	28 (70%)	(CT+TT) vs. CC	0.000*	Reference Genotype 3.200 (1.987-5.155)
CT	33 (66%)	2 (5%)			
TT	15 (30%)	10 (25%)			
Allele frequency					
Allele C	3 (6%)	30 (75%)	T vs. C	0.000*	Reference Allele 3.760 (2.188-6.461)
Allele T	47 (94%)	10 (25%)			
rs1553316: T>C					
Genotype frequency					
TT	6 (12%)	10 (25%)	(TC+CC) vs. TT	0.109	Reference Genotype 1.173 (0.955-1.442)
TC	1 (2%)	0 (0%)			
CC	43 (86%)	30 (75%)			
Allele frequency					
Allele T	7 (14%)	10 (25%)	C vs. T	0.185	Reference Allele 1.147 (0.929-1.416)
Allele C	43 (86%)	30 (75%)			
rs12522248: A>G					
Genotype frequency					
AA	41 (82%)	32 (80%)	(AG+GG) vs. AA	0.810	Reference Genotype 0.900 (0.382-2.120)
AG	8 (16%)	4 (10%)			
GG	1 (2%)	4 (10%)			
Allele frequency					
Allele A	49 (98%)	36 (90%)	G vs. A	0.100	Reference Allele 0.200 (0.023-1.720)
Allele G	1 (2%)	4 (10%)			

*Significant ($P \leq 0.05$) values are in bold.

associated with coronary heart disease and ischemic stroke (Zhang et al., 2018). However, this SNP was not associated with systemic lupus erythematosus in Chinese population (Li et al., 2011). In addition, Grabmer *et al.* examined the association of this SNP and rs1553316 with multiple sclerosis in Western Austria, but no significant association was demonstrated (Grabmer et al., 2010).

Table 3. Haplotype frequencies in AKI patients and control subjects

Haplotype	AKI N (%)	Control N (%)	P- value	OR (95% CI)
CTA	46 (92%)	4 (10%)	0.000*	0.089 (0.035- 0.229)
GCA	2 (4%)	6 (15%)	0.132	1.129 (0.980- 1.302)
CTG	1 (2%)	2 (5%)	0.583	1.032 (0.951- 1.119)
CCA	1 (2%)	0 (0%)	1.000	0.980 (0.942- 1.020)

*Significant ($P \leq 0.05$) values are in bold

In order to investigate the potential association between the studied SNPs and AKI, haplotype analyses were performed. Subsequent haplotype analysis revealed that 3 SNPs (rs1401877734, rs1259856748, rs12522248) formed one haplotype block. An overall of 4 haplotypes were generated, among which only one haplotype (CTA) showed a significant difference between patients and controls and it seems to provide a higher risk for the acute kidney injury occurrence, while the others were not shown to confer a

protective effect against the disease. The results are shown in Table 3. We also examined the association between *KIM-1* SNPs and different parameters including age, gender, BMI, blood pressure, smoking, and other diseases, such as diabetes, anemia, liver and pulmonary disease. Differences in these parameters between AKI patients and controls are shown in Table 4. No association was observed ($P > 0.05$) implying that the effect of *KIM-1* gene polymorphism is independent of these parameters in AKI.

In addition, the association between *KIM-1* genetic polymorphisms and serum creatinine and urea levels was analyzed as shown in Table 5. None of these SNPs was found to be significantly associated with increased creatinine and urea levels in serum. Knowing that creatinine is secreted by proximal tubule (Musso et al., 2009) and that urea is partially reabsorbed by this tubule (Gowda et al., 2010), our results suggest that the genetic polymorphism of *KIM-1* may lead to alterations in its genetic expression in the proximal tubules, which in turn may affect creatinine tubular secretion and urea tubular reabsorption and thereby altering their serum levels. Haplotype frequencies among AKI patients and their association with serum creatinine and urea were investigated and shown in the Table 6. Analyzing these haplotypes, only haplotype CTA showed a significant difference between AKI patients and controls ($P < 0.05$), providing a higher risk for AKI. Although none of the studied SNPs showed a significant correlation with serum creatinine and urea levels, the carriers of CTA haplotype block consisting of three SNPs had the highest levels of these parameters.

Table 6. Association between haplotypes in *KIM-1* and serum parameters

Haplotype	Samples number (%)	Creatinine ^a (mg/dL)	P-values	Urea ^a (mg/dL)	P-values
CTA	46 (92%)	2.6±1.14	0.009*	88.5±18.8	0.007*
GCA	2 (4%)	1.8±0.9	0.999	84.0±62.3	0.840
CTG	1 (2%)	3.5	0.755	207	0.283
CCA	1 (2%)	3.08	0.917	96	0.652

*Significant ($P \leq 0.05$) values are in bold. ^aValues are shown as mean ± standard

Table 4. Baseline parameters and clinical data of AKI patients and controls

Parameters	AKI Patients (n=50)		Control (n=40)	
	Yes (%)	No (%)	No (%)	Yes (%)
Any family member with kidney diseases	15 (30%)	35 (70%)	6 (15%)	34 (85%)
Heart disease	13 (26%)	37 (74%)	16 (40%)	24 (60%)
Diabetes	12 (24%)	38 (76%)	10 (25%)	30 (75%)
Blood pressure problems	20 (40%)	30 (60%)	20 (50%)	20 (50%)
Anemia	17 (34%)	33 (66%)	14 (35%)	26 (65%)
Severe dehydration	9 (18%)	41 (82%)	8 (20%)	32 (80%)
Weak immunity	10 (20%)	40 (80%)	6 (15%)	34 (85%)
Liver problems	2 (4%)	48 (96%)	6 (15%)	34 (85%)
Pulmonary disease	9 (18%)	41 (82%)	12 (30%)	28 (70%)
Vision problem	19 (38%)	31 (62%)	22 (55%)	18 (45%)
Any surgery or organ transplantation	30 (60%)	20 (40%)	22 (55%)	18 (45%)
Received blood transfusion	23 (46%)	27 (54%)	14 (35%)	26 (65%)
Currently a smoker	19 (38%)	31 (62%)	20 (50%)	20 (50%)
Drink caffeinated beverages	40 (80%)	10 (20%)	32 (80%)	8 (20%)
Drink alcohol	0 (0%)	50 (100%)	2 (5%)	38 (95%)

Table 5. Differences in the value of serum creatinine and urea among AKI patients stratified by different *KIM-1* genotypes

SNP	Genotype	Samples number (%)	Creatinine ^a (mg/dL)	P-values	Urea ^a (mg/dL)	P-values
rs1401877734: G>C	GG	2 (4%)	3.15±0.66	0.71	115.5±31.45	0.569
	GC	39 (78%)	3.85±0.33		133.3±10.58	
	CC	9 (18%)	4.1±0.82		177.22±28.15	
rs781388022: C>T	CC	13 (26%)	2.96±0.15	0.228	107.01±12.2	0.082
	CT	27 (54%)	4.29±0.46		146.96±12.99	
	TT	10 (20%)	3.91±0.76		166.5±26.84	
rs1259856748: C>T	CC	2 (4%)	3.15±0.68	0.71	115.5±32.44	0.569
	CT	33 (66%)	4.01±0.38		142.67±11.82	
	TT	15 (30%)	3.66±0.5		139.07±20.52	
rs1553316: T>C	TT	6 (12%)	3.1±0.27	0.612	105.17±14.65	0.250
	TC	1 (2%)	2.4		71	
	CC	43 (86%)	4.01±0.33		147.05±11.05	
rs12522248: A>G	AA	41 (82%)	3.8±0.32	0.495	130.1±10.34	0.052
	AG	8 (16%)	4.26±0.9		185.5±31.14	
	GG	1 (2%)	3.5		207	

^aValues are shown as mean ±standard deviation

Conclusion

This is the first study which showed the association between polymorphisms in *KIM-1* and AKI. In this study, differences in the genotypic and allelic frequencies of *KIM-1* SNPs between controls and patients were obtained. Three SNPs and the CTA haplotype within exon 4 of *KIM-1* are shown to be associated with susceptibility to AKI in Lebanese population. The mechanism by which *KIM-1* polymorphism contributes to conferring susceptibility to acute kidney injury remains to be elucidated. However, the present study suggests that *KIM-1* may be useful prognostic factor for acute kidney injury. Future studies, with a larger number of participants are needed to clarify the role of genetic variation in determining the risk of AKI among the Lebanese and other populations.

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Conflict of Interest

The authors state there is no conflict of interest.

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