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Matrix Metalloproteinase-3 E45K Polymorphism is Associated with the Risk of Sepsis in the Turkish Population: A Preliminary Study

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Abstract

Aim: Sepsis is a condition characterized by an abnormal immune response triggered by infection, leading to high mortality rates. Matrix metalloproteinases (MMPs), known for their proteolytic activity under physiological conditions, also contribute to the inflammation resulting from the abnormal immune response observed in sepsis. This study aimed to investigate the effect of *MMP-3* gene variation on the risk of developing sepsis in the Turkish population.

Study Design: We conducted a case-control study.

This study examined the *E45K* and *T102T* polymorphisms of the *MMP-3* gene using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) methods in 78 sepsis patients and 81 healthy controls from the Turkish population.

Results: The results revealed a significantly higher frequency of the *E45K G* allele (p=0.004) in sepsis patients compared to healthy controls. Additionally, an increased frequency of the *E45K AA* genotype was observed among healthy controls (p=0.004). Moreover, we found that having the *E45K GG* genotype (p<0.001) increased the risk of developing sepsis in patients with Chronic Obstructive Pulmonary Disease (COPD). Accordingly, irrespective of the presence or absence of COPD, carrying the G allele, whether homozygous or heterozygous, appears to be a risk factor for sepsis. However, no significant changes in allele frequencies or genotypes were observed for the *T102T* polymorphism in both groups.

Conclusions: Our primary findings indicate that carrying the *E45K G* allele may be associated with an increased risk of sepsis.

Keywords: COPD; Matrix metalloproteinase-3; Polymorphism; Sepsis.

Introduction

Sepsis is a life-threatening condition characterized by a high mortality rate, resulting from an impaired host response to infection.[1] This response to bacterial, viral, or fungal infections is characterized by simultaneous excessive inflammation due to strong activation of the immune system, and immune suppression. The

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development of initial hyper-inflammation, induced by the excessive release of proinflammatory cytokines, causes tissue damage. A subsequent reduction in proinflammatory cytokine production, due to the apoptosis of innate immune cells, leads to hypo-inflammation.[2-4] This imbalance in the immune response leads to organ failure and predisposes patients to secondary infections that worsen the clinical picture. Any patient hospitalized for any reason who acquires an infection is potentially at risk of developing sepsis.[5] Furthermore, the majority of these patients have at least one chronic condition, such as Chronic Obstructive Pulmonary Disease (COPD), diabetes, chronic liver disease, or chronic kidney disease. On the other hand, respiratory tract infections are the most common cause of sepsis in patients and are associated with high mortality.[6] In COPD patients, disruption of the barrier function of the respiratory tract, through loss of extracellular matrix (ECM) integrity, makes the area more susceptible to infections, leading to sepsis.[7]

Although current definitions suggest sepsis primarily involves a dysregulated inflammatory response, it is actually a condition characterized by highly complex changes at the molecular and gene expression levels, causing multi-organ dysfunction.[5] These changes can occur in molecules that allow for the early diagnosis of sepsis patients, before symptoms appear, and these molecules may play an important role in the pathology of the primary disease that eventually leads to sepsis.

Matrix metalloproteinases (MMPs) are zinc-containing endoproteases that have proteolytic activity capable of degrading ECM or non-ECM proteins.[8] In addition to the many physiological roles of MMPs, such as cell proliferation and differentiation, wound healing, embryogenesis, angiogenesis, and apoptosis, any dysfunction in these enzymes can contribute to pathological conditions such as cardiovascular diseases, arthritis, tissue fibrosis, and cancer.[9] However, MMPs have been implicated in the inflammation that occurs during certain diseases or injuries. Pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), secreted from infected or damaged cells in response to microbial triggers or tissue damage, are recognized by pattern-recognition receptors (PRRs) such as Toll-like receptors (TLR) or Nucleotide-binding Oligomerization Domain-like receptors (NOD-like receptors or NLR) on tissue-resident macrophages or mast cells. This recognition triggers the production of inflammatory modulators such as cytokines, chemokines, eicosanoids, and proteolytic enzymes, attracting immune cells to the site of infection or damage.[10,11] At this juncture, a variety of MMPs are reported to play a key role in different aspects of the inflammatory process.[12] For instance, MMP-2, *MMP-3*, and MMP-9 increase vascular permeability by proteolysis of tight junction proteins in the endothelial barrier, facilitating the migration of neutrophils and monocytes to the site, while MMP-10 and MMP-19 promote the resolution of acute inflammation and tissue repairing by enabling the production and migration of anti-inflammatory macrophages to the tissue.[13,14] In many diseases where inflammation plays a pivotal role in development, MMPs contribute to the pathology of sepsis, characterized by excessive acute inflammation resulting from strong proinflammatory activation. Studies have indicated an increase in both plasma levels and messenger ribonucleic acid (mRNA) expression of MMPs in patients with sepsis. High levels of *MMP-3*, 8, and 10 in plasma have been observed in parallel with the levels of neutrophils and C-reactive protein (CRP) in patients in the intensive care unit, while increased levels of MMP-2 and 13 have been noted in survivors compared to non-survivors. D Avila-Mesquita et al.[15] demonstrated that Coronavirus Disease 2019 (COVID-19) mortality was associated with elevated levels of MMP-2 and MMP-9. Furthermore, age, hypertension, body mass index (BMI), and levels of MMP-2 and MMP-9 were identified as better predictors of mortality during hospitalization than the Simplified Acute Physiology Score III (SAPS3) and the Sequential Organ Failure Assessment (SOFA) scores at hospital admission. In another study, sepsis patients carrying the *MMP-3 (-1612 5A/6A)* exhibited higher plasma MMP-3 levels compared to those with the *5A5A* genotype and the control group. Additionally, levels of MMP-3, 8, and 10 decreased progressively during follow-up in the intensive care unit.[16,17] In summary, these findings suggest that MMPs can play a crucial role in the clinical prognosis, progression, and monitoring of sepsis.

The activity of MMPs is regulated through various mechanisms including epigenetically, transcriptionally, or post-transcriptionally at the gene expression level, as well as through extracellular or proteolytic means in both diseased or healthy conditions. Therefore, to elucidate the role of MMPs in the pathogenesis of sepsis, it is essential to investigate the functional polymorphisms affecting their gene expression. In the present study, we evaluated the *E45K* (rs679620) and *T102T* (rs41380244) polymorphisms of *MMP-3* in sepsis patients.

Materials and Methods

Study Group

The study group comprised 78 patients (mean age: 65.37±10.39 years) diagnosed with sepsis at Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Department of Anesthesiology and Reanimation. As a control group, 81 healthy individuals (mean age: 62.58±9.92 years) without any signs of sepsis were selected. The study was approved by the ethics committee Haydarpasa Numune Training and Research Hospital (Ethical Approval Number: HNEAH-KAEK 2021/KK/326, Date: 10/01/2022), and written informed consent was obtained from all participants or their legal representatives before participating in the study.

Deoxyribonucleic Acid (DNA) Isolation

Peripheral blood samples from all participants were collected into Ethylenediaminetetraacetic acid (EDTA)-containing tubes. DNA isolation was performed according to the instructions of the Genomic DNA Isolation Kit (Invitrogen, Waltham, Massachusetts, USA).

Genotyping MMP-3 Polymorphism

The *MMP-3-E45K* and *T102T* polymorphisms were genotyped using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) methods. The primer sequences for the *E45K* and *T102T* polymorphic sites are as follows, respectively:

F: 5′-AAATTTGCCATTATTTCAGCAAG-3′

R: 5′-CCCCTCTGAACCATTACCTG-3′

F: 5′-GTTCCTTGGATTGGAGGTGA-3′

R: 5′-CCTGTAGGAGAAAAATTGAAGCA-3′

For the *E45K* polymorphism, the PCR conditions were as follows: initial denaturation at 94ºC for 5 minutes, followed by 35 cycles denaturation at 94ºC for 30 seconds, annealing at 59ºC for 30 seconds, extension at 72ºC for 30 seconds, and a final extension at 72ºC for 7 minutes. PCR products were digested with the TaqI restriction enzyme at 60ºC for 3 hours. The digestion product was examined by electrophoresis on a 2% agarose gel, identifying 399 bp for the *AA* genotype, 236 and 163 bp for the *GG* genotype, and 399, 236, and 163 bp for the *AG* genotype. For the *T102T* polymorphism, the PCR conditions were: initial denaturation at 94ºC for 5 minutes, 35 cycles of denaturation at 94ºC for 30 seconds, annealing at 58ºC for 30 seconds, extension at 72ºC for 30 seconds, and a final extension at 72ºC for 7 minutes. PCR products were digested with the AclI restriction enzyme at 37ºC for 3 hours. The digestion product was examined by electrophoresis on a 2% agarose gel, identifying 237 bp for the *CC* genotype, 139 and 98 bp for the *GG* genotype, and 237, 139, and 98 bp for the *CG* genotype.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 21.0 software package (SPSS Inc., Chicago, USA). P-values less than 0.05 were considered statistically significant. Differences in genotypes and allele frequencies between the study and control groups were determined using the Chi-square (χ^2) test. Fisher's exact test was used when the expected cell value was less than five. Odds ratios (ORs) and confidence intervals (CIs) were calculated to estimate the relative risk.

Results

Demographic and clinical parameters of the study groups are shown in Table 1. Table 2 presents the *MMP-3 E45K* and *T102T* genotype and allele distributions in our study groups. It was observed that the frequency of carrying the *E45K AA* genotype was significantly higher in the healthy group compared to the patient group (p=0.004, χ^2=8.182, OR=1.79, 95% CI=1.18-2.71). Additionally, the frequency of carrying the *G* allele was significantly higher in the patient group compared to the control group (p=0.004, χ^2=8.343, OR=2.6, 95% CI=1.35-5.03). No statistical difference was observed when comparing the groups according to *MMP-3 T102T* genotype

Table 1. Demographical and clinical parameters of study groups

Parameters	Patients with Sepsis (n=78)	Controls (n=81)	p
Age (year)	65.37±10.39	62.58±9.92	>0.05
Weight (kg)	77.83±11.70	74.11±19.26	>0.05
Height (cm)	167.13±10 09	168.21±8.56	>0.05
CRP (mg/dl)	17.47±5.43	-	-
Creatinine (mg/dl)	2.07±1.43	-	-
pH	7.35±0.10	-	-
Lactate (mEq/L)	3.82±3.66	-	-
LDH (U/L)	487.14±256.37	-	-

Data are presented as mean±SD.

and allele distribution. In addition to Single Nucleotide Polymorphism (SNP) analysis, haplotypes were evaluated for association with sepsis. Table 3 displays the haplotype analysis. Our findings indicate that the *CA (T102T A, E45K A)* and *CG (T102T C, E45K G)* haplotypes are associated with sepsis (p=0.011, p=0.003, respectively).

When examining the relationship between clinical and demographic parameters and genotypes, significant findings were observed for the *E45K* variant and COPD in patients. It was found that carrying the *E45K GG* genotype increases the risk of sepsis in patients with COPD (p<0.001, χ^2=14.26, OR=7.0, 95% CI=2.41-20.28), while carrying the *AG* genotype (p=0.005, OR=3.92, 95% CI=1.28-11.98) and the *A* allele (p<0.001, χ^2=14.26, OR=3.57, 95% CI=1.75-7.27) reduces the risk of COPD (Table 4).

Table 2. Genotype and allele distributions of MMP-3 E45K and T102T in study groups

MMP-3 E45K	Patients with Sepsis (n=78)	Controls (n=81)
Genotypes		
AA	22 (28.2%)	41 (50.6%)*
GG	28 (35.9%)	20 (24.7%)
AG	28 (35.9%)	20 (24.7%)
Alleles		
A	72 (46%)	102 (63%)
G	84 (54%)**	60 (37%)
MMP-3 T102T	**Patients with Sepsis (n=78)**	**Controls (n=81)**
Genotypes		
CC	66 (84.6%)	65(80.2%)
GG	-	-
CG	12(15.4%)	16(19.8%)
Alleles		
C	144 (92.3%)	146(90.1%)
G	12 (7.7%)	16(9.9%)

*p=0.004, **p=0.004.

Also, we examined the distribution of the *E45K* variant in sepsis patients without COPD and in healthy controls. We observed that the frequencies of the *E45K AG* genotype (p=0.009, χ^2=6.80, OR=2.62, 95% CI=1.26-5.48) and the *G* allele (p=0.028, χ^2=4.84, OR=2.23, 95% CI=1.08-4.58) were elevated in sepsis patients without COPD compared to healthy controls. Additionally, the *AA* genotype was more prevalent in healthy controls (p=0.028, χ^2=4.84, OR=1.60, 95% CI=1.02-2.51) (Table 5).

Table 4. Distribution of E45K variants according to having COPD in patients.

MMP-3 E45K	COPD (+) (n=24)	COPD (-) (n=54)
Genotypes		
AA	5 (22.7%)	17 (77.3%)
GG	16 (57.1%)*	12 (42.9%)
AG	3 (10.7%)	25 (89.3%)**
Alleles		
A	13 (27%)	59 (54.6%)*
G	35 (73%)	49 (45.4%)

*p<0.001, **p=0.005.

Table 5. Distribution of E45K variants according to having COPD (-) patients and controls.

MMP-3 E45K	Patients COPD (-) (n=54)	Controls (n=81)
Genotypes		
AA	17 (31.5%)	41 (50.6%)**
GG	12 (22.2%)	20 (24.7%)
AG	25 (46.33%)***	20 (24.7%)
Alleles		
A	59 (54.6%)	102(62.9%)
G	49 (45.4%)*	60 (37.1%)

*p=0.028, **p=0.028, ***p=0.009.

Table 3. The frequencies of haplotype of MMP-3 gene in study groups.

Haplotype Associations	Frequencies	Case, Control Ratios	X^2	p
CA	0.492	0.420; 0.562	6.44	0.011*
CG	0.420	0.503; 0.339	8.80	0.003**
GA	0.055	0.042; 0.067	1.01	0.313
GG	0.033	0.035; 0.031	0.03	0.847

Discussion

Sepsis is a severe condition with a high incidence in hospitalized patients, leading to serious consequences such as multiorgan failure and ultimately death. Both immune and non-immune modulators are involved in the complex pathogenesis of sepsis, making it crucial to understand their roles for effective management.[18] In this study, we examined two SNPs of *MMP-3; E45K* (rs679620) and *T102T* (rs41380244), which we believe may contribute to the pathogenesis of sepsis in Turkish patients.

Inflammation, resulting from an uncontrolled or abnormal immune response to infections, is a major cause of the poor outcomes observed in sepsis. Numerous studies have demonstrated that MMPs are one of the modulators that contribute to this inflammatory condition and the pathology of sepsis by regulating the activation of cytokines and chemokines through their primary function of proteolytic degradation.[16,19,20] Among these MMPs, MMP-3 has been identified as playing a key role in inflammatory conditions across various diseases, including sepsis. Specifically, the well-studied polymorphism *(-1612 5A/6A)* in the promoter region of the *MMP-3* gene has been associated with conditions such as rheumatoid arthritis,[21] atherosclerosis,[22] and cancer. Collazos et al.[23] reported an enhancing effect of the *6A* allele carriers of *MMP-3 (-1612 5A/6A)* on MMP-3 plasma levels in patients with severe bacterial sepsis. Similarly, another study demonstrated that patients carrying the variant *(-1612 5A/6A)* on the first day of hospitalization in the intensive care unit exhibited elevated plasma levels of neutrophils, leukocytes, CRP, and MMP-3.[16] Fiotti et al.[20] observed a higher prevalence of viral sepsis in patients carrying the *MMP-3* rs3025058 *6A* allele. In connection with this, considering that MMP-3 translocates to the nucleus and increases Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation in the antiviral immune response pathway,[24] this suggests that diverse inflammation pathways are involved in the various etiologies of sepsis.

Previous studies have associated the *E45K* polymorphism rs679620 with conditions such as ischemic stroke,[25] periodontitis,[26] tendinopathy, and knee injury;[27] however, no study has yet shown its association with sepsis. In this research, we reported the association of MMP-3 polymorphisms *E45K* and *T102T* with sepsis. Regarding allele distribution, we noted a significant prevalence of the *E45K G* allele in patients, while no significant difference was observed in the allele distribution for the *T102T* variant. Moreover, we found that the risk of COPD is significantly elevated in sepsis patients with the *GG* genotype compared to carriers of the *A* allele. Previous research indicates that MMPs cause the deposition of extracellular matrix (ECM) components in the lungs of COPD patients, thereby increasing inflammation through monocyte infiltration.[28] It has been shown that the *6A6A* genotype in the *–1171 5A/6A* polymorphism of *MMP-3* does not pose a risk for the development of COPD but is associated with severe disease.[29] Furthermore, Bchir et al.[30] have linked the *6A6A* and *GG* genotypes in the polymorphisms of *MMP-3 (-11715A/6A)* and *Lys45Glu (A/G)* with reduced lung function and elevated serum MMP-3 levels in COPD patients). Additionally, studies on the impact of sepsis on COPD patients' outcomes have found that those with COPD who developed sepsis had a higher risk of exacerbations, pneumonia, and mortality compared to those without sepsis.[31] Therefore, our results may indicate that the *GG* homozygous genotype exacerbates lung inflammation and causes sepsis in COPD patients. However, the higher frequency of *G* allele carriers in sepsis patients without COPD, compared to healthy controls, has shown us that the *MMP-3 E45K* genotype is also a risk for sepsis independent of COPD.

Our study has several limitations, including a relatively small sample size and the lack of serum MMP-3 level measurements.

Conclusion

In this study, we determined for the first time in the literature that the *G* allele of the *E45K* (rs679620) variant is associated with an increased risk of sepsis. Moreover, the *GG* genotype further elevates the risk of sepsis in COPD patients.

Ethics Committee Approval: The study was approved by the Ethics Committee of Haydarpasa Numune Training and Research Hospital (Approval Number: HNEAH-KAEK 2021/KK/326, Date: 10/01/2022).

Informed Consent: Consent form was obtained from the patients included in the study or from their relatives.

Peer-review: Externally peer-reviewed.

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