REVIEW ARTICLE

Association Between TNF-α (-308G →A) Gene Polymorphism and Burn Patient with Sepsis

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ABSTRACT

Burning is damage to the skin and loss of the primary barrier of infection. Burned skin is at risk of infection as long as the barrier is absent. If not treated, infection caused by serious burns can be life-threatening and lead to sepsis. Sepsis is a life-threatening organ dysfunction due to the anti-infection host not responding; early treatment is critical. Sepsis is the leading cause of death, resulting in up to 50 to 60% of burn injury deaths. Therefore, the present study aimed to diagnose sepsis in burn patients and to study the relationship between TNF-α (-308G →A) gene polymorphism and burn patient with sepsis. Recorded results showed that procalcitonin (ng/mL) (PCT) significantly higher in sepsis than in without sepsis burn patients group ($p < 0.05$), 9.16 ± 5.07 versus 0.57 ± 1.27 respectively. The genotypes relative frequency in burn patient with sepsis were as follow : GG (40 %), GA (45%) and AA (15%); while in burn patient without sepsis subjects : GG (53.3%), GA (33.3%) and AA (13.3%). G allele is higher frequency (62.5%) in burn patients with sepsis than A allele (37.5%). The presence of heterozygous GA genotype in the TNF-α-308 was associated with sepsis of burn patient

Keywords: Burn, Sepsis and procalcitonin test, Tumor necrosis factor –alpha (TNF-α).

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INTRODUCTION

Burn is defined as damage due to software of heat/chemicals to the external or internal surface of the frame, which motives the destruction of tissues.[1] As a result, between 50 to 75% of burn-related deaths belong to direct infection by microorganisms and its complications.[2] Skin is a protective body from infections, and it is the first line of defense against microbial. In burns, the body is loose skin and leads to acute infection due to suppress the immune system, and these infections can escape into the bloodstream and distribution during the circulatory system, causing bacteremia and septic shock.[3] Burn wound infections are a number one problem for the duration of the treatment pathway because of their ability to create extreme difficulties to increase mortality.[4]

Sepsis can be defined as systemic inflammatory response syndrome (SIRS) caused by infection, and the infection is bacteria, viral, fungal, and protozoan, but the bacteria is most commonly.[5,6] SIRS is a caused nonspecific inflammatory response for infectious or noninfectious origin also produced ischemia, inflammation, burns, trauma, and infection.[7] Sepsis can also be defined as life-threatening when the body's response to infection.[8] The reported sepsis over 18 million each year, and 30% of them in burn infections.[9] A diagnosis of sepsis were based on common signs and symptoms include temperature > 38°C or < 36°C, respiratory rate > 20 breaths per minute, heart rate > -leukocytosis] are less relevant in burns because those signs and symptoms nonetheless exist on this patient.[10]

Single nucleotide polymorphisms (SNPs), variations in a nucleotide at a specific chromosome location, have been linked to sepsis susceptibility and prognosis differences.[11] Among these diverse cytokines, tumor necrosis factor-α (TNF-α) has attracted considerable attention. The promoter of single nucleotide polymorphisms (SNP) at position - 308 (G to A substitution) of the TNF-α gene has been demonstrated to play a significant role in the pathogenesis of sepsis and its complications after burn injury.[12] They identified specific toll-like receptor 4, and TNF-α SNPs are associated with an increased risk of sepsis after burn injury.[13] TNF -α is a pro-inflammatory cytokine produced by lymphocytes and macrophages. Mainly TNF-α appears to participate in the pathogenesis of the obesity-induced type 2 diabetes mellitus (T2 DM) and interventional radiology (IR), autoimmune disease, septic shock, rheumatoid arthritis, and other inflammatory disorder.[14]

MATERIALS AND METHODS

It is a case-control study in which 70 burn patients, with ages ranging from 15–55 years, observed in the specialized

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centre for burns of Al–Diwaniyah from March 2019 to the end of November 2019. Sera and whole blood were collected from each participant, noting that the sera were used to determine PCT test, white blood cell for diagnostic sepsis for all specimens, while whole blood was used to extract DNA.

DNA extraction was used to detect SNPs in TNF-α ((TNF-α -308G →A)) with the use of amplification refractory mutation system polymorphism PCR (ARMS – PCR) technique, which is a rapid, uncomplicated and sensitive method. ARMS – PCR was performed by Thermocycler (Analytic Jena, Germany), gene polymorphism primers were designed by Sun M, *et al*,[15] and these primers were provided from (Bioneer Company, Korea).

The ARMS-PCR master mix of TNF-α gene polymorphism was done two reactions for each sample (G allele master mix reaction) and (A allele master mix reaction) using AccuPower^{TM} PCR PreMix (Bioneer, Korea) were employed. G allele master mix reaction: five µL DNA, 2 µL of G allele primer (10 pmol), 2 µL Reverse primer (10 pmol) and 11 µL PCR. An allele master mix reaction: five µL DNA, 2 µL of A allele primer (10 pmol), 2 µL Reverse primer (10 pmol) and 11 µL PCR. After that, these ARMS-PCR master mix reaction components mentioned above, placed in standard PCR tubes containing the PCR PreMix as lyophilized materials containing all other components needed for PCR reaction such as (Taq DNA polymerase, dNTPs, Tris. HCl pH: 9.0, KCl, $MgCl_2$, stabilizer, and loading dye). Then all PCR tubes transferred into the Exispin vortex centrifuged at 3000 rpm for 3 minutes. They were then placed in PCR Thermocycler (Mygene, Korea).

The PCR conditions consisted of an initial denaturation step at 95°C for 5 minutes, 10 cycles of incubation at 95°C for 15s, 65°C for 50 seconds and 72°C for 40 seconds, followed by 20 cycles of incubation at 95°C for 20 seconds, 56°C for 50 seconds and 72°C for 50 seconds, with a final extension at 72°C for 5 minutes.

The PCR products were analyzed by electrophoresis on 2% agarose gel containing 3 µL of ethidium bromide stain. Then bands were seen by UV ray (ATTA, South Korea) Figure 1.

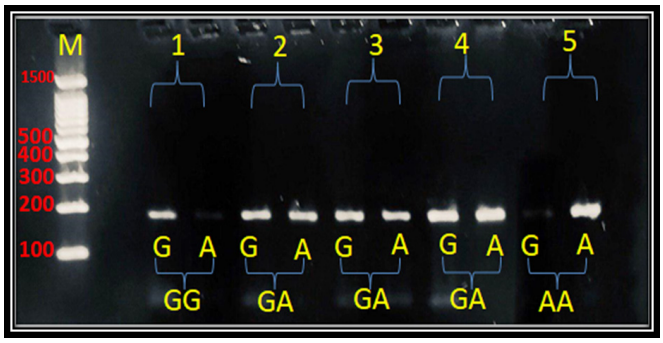

Figure 1: Agarose gel electrophoresis image that shows the ARMS-PCR product analysis of TNF–α (-308 G →A) in the sample. ARMS-PCR product was analyzed by 2% agarose gel. Where M: marker (100bp – 1500bp).

The difference between the frequency of genotypes and alleles in burn patients with sepsis and burn patients without sepsis groups was determined by chi-square test using SPSS V.24 program was used in statistical analysis of the data software. $p < 0.05$ was considered significant. A logistic regression test was used to estimate the Odds ratio (OR) and confidence interval 95% (CI).

RESULTS

The diagnosis of sepsis was based on the American Burn Society (ABS) criteria Biomarker (procalcitonin, white blood cells and temperature body) values were available for 40 burn patients with sepsis and 30 burn patients without sepsis according to Greenhalgh D G, *et al*.[10] The result biomarkers levels in sepsis and without sepsis burn patients and all other variables showed statistical differences between both groups, as shown Table 1.

The genetic polymorphism of TNF -α gene was determined at one position; TNF–α -308 G →A, which was present with three genotypes (GG, GA, and AA) in burn patients with sepsis and burn patient without sepsis.

ARMS-PCR method was used to genotyping TNF–α -308 G →A in burn patients with sepsis and burn patients without sepsis. The PCR product size was 184 bp. The positive amplification of both PCR reactions exhibited a GA genotyping. In contrast, positive amplification in only the first PCR reaction exhibited a GG genotype, and finally, the positive amplification in the second reaction only showed an AA genotype of TNF–α -308 G →A as shown in the Figure 1. TNF alpha genotype frequency distribution in burn patients with sepsis and burn patients without sepsis groups is shown in Table 2. The genotypes relative frequency in burn patient with sepsis were as follow: GG (40 %), GA (45%) and AA (15%); while in burn patient without sepsis subjects: GG (53.3%), GA (33.3%) and AA (13.3%). G allele is the higher frequency (62.5%) in burn patient with sepsis than A allele (37.5%)

There was no significant difference in the TNF alpha allele frequency distribution between burn patient with sepsis and burn patient without sepsis groups ($p = 1.400$), as shown in Table 3.

DISCUSSION

When sepsis signs may be present in the absence of actual infection, especially in burns, it is difficult to diagnose the

Table 1: Biomarkers levels in sepsis and without sepsis burn patients

Biomarker	*Sepsis n = 40*	*Without sepsis n = 30*	*p-value*
Procalcitonin (ng/ml)	9.16 ± 5.07	0.57 ± 1.27	0.01*
WBC cells ($1*10^3$/cc)	12.87 ± 5.88	7.30 ± 3.46	0.038*
temperature	38.43 ± 2.43	36.82 ± 0.19	0.47
Blood culture	positive	Negative	

n: number of cases; SDL standard deviation; *significant at $p < 0.05$

Table 2: TNF α genotype frequency distribution in burn patient with sepsis and burn patient without sepsis groups

	Study groups						*95% CI for OR*	
TNF-α SNP	*burn patient with sepsis N=40*	*burn patient without sepsis N=30*	*Total*	*P-value*	*B*	*OR*	*Lower Bound*	*Upper Bound*
AA	6 15.0%	4 13.3%	10 14.3%	0.582	0.405	1.500	0.355	6.347
GA	18 45.0%	10 33.3%	28 40.0%	0.267	0.588	1.800	0.637	5.083
GG	16 40.0%	16 53.3%	32 45.7%	Reference category				
P-value	0.014	0.109						

Table 3: TNF alpha allele frequency distribution in burn patient with sepsis and burn patient without sepsis groups

	Study groups					*95% CI for OR*	
TNF-α	*Burn patient with sepsis*	*Burn patient without sepsis*	*Total*	*P-value*	*OR*	*lower*	*upper*
A	30 37.5%	18 30.0%	48 34.3%	1.400	0.686	2.859	1.400
G	50 62.5%	42 70.0%	92 65.7%				
Total	80 100.0%	60 100.0%	140 100.0%				
P-value	0.025	0.002					
RR 95% CI	1.150 0.86–1.53	0.821 0.53–1.26					

sepsis. This problem induces inappropriate administration of antibiotics, with risk of resistance and rise of cost. The search for a marker defining risk for infection among burned people is of clinical interest because they may benefit from rapid diagnosis and treatment. The use of PCT combined with other laboratory and clinical sepsis biomarkers certainly reinforces the diagnostic power.[16] PCT is synthesized physiologically by thyroid C cells but, in sepsis, has an extra-thyroidal origin. Parenchymal cells (including liver, lung, kidney, adipocytes, and muscle) provide the enormous tissue mass and the principal source of circulating PCT in sepsis.[17]

The results of this study showed PCT significantly higher in sepsis than in without sepsis burn patients group ($p < 0.05$), 9.16 ± 5.07versus 0.57 ± 1.27 respectively and agreement with a study by Barati *et al*., who demonstrated that a significantly higher PCT level was observed among participants with sepsis compared with those without sepsis (8.45 7.8 vs. 0.5 1.0, respectively; $p < 0.001$[18] and also study by Lavrentieva *et al*. showed both PCT and CRP plasma concentrations were statistically significantly higher among patients with sepsis compared to SIRS (non-infected) and negative patients.[19] Jekarl *et al.* found that an elevation in PCT (ng/mL) in sepsis and without sepsis burn patients groups.[20]

The others results suggest that serum PCT is a useful biomarker (AUC = 0.92) for early diagnosis of sepsis in burn patients. However, the results should be used with caution, because of obvious heterogeneity among those studies.[21]

Main white blood cells (WBC) count of sepsis was (12.87 ± 5.88), and WBC of without sepsis (7.30 ± 3.46). There was significant difference in sepsis and without sepsis burn patients. The WBC count, neutrophil percentage or changes in these values were not clinically reliable in predicting bloodstream infection in burn cases.[22]

Blood microbiological cultures can help the identification of systematic bacterial infection, but the results often reported late and yield false positive or negative results.[23] Traditional markers such as C-reactive protein (CRP) and WBC are too weak to accurately identify sepsis in the burned patient, because of the baseline inflammatory response and immunopathies.[22,24]

Single nucleotide polymorphisms (SNPs) in the genes encoding these cytokines may be related to the risk of sepsis, and may even play roles in its pathogenesis.[25,26] Among these diverse cytokines, tumor necrosis factor-α (TNF-α) has attracted considerable attention. TNF-α is an intensively studied pro-inflammatory cytokine released mainly by activated neutrophils and macrophages that helps regulate the mammalian immune response and cellular homeostasis.[27]

In the present study show heterozygous GA genotype was significantly higher in burn patients with sepsis than in control (burn patient without sepsis) group 20 out of 40 versus 6 out of 30, respectively. The AG genotype was a risk factor with an odds ratio of 1.800 (0.637–5.083). The study showed that GA genotype distribution of TNF-α gene rs1800629 polymorphism in two groups had statistical significance, indicating an obvious association with the susceptibility of sepsis ($p = 0.035$, OR = 2.501, 95% CI = 1.405–5.988). Besides, A allele was observed high frequencies in cases compared with controls, demonstrating a positive relationship with sepsis susceptibility ($p = 0.030$, OR = 2.289, 95% CI = 1.063–4.929). These results demonstrated that TNF-α gene rs1800629 polymorphism correlated with sepsis susceptibility.[28]

The -308G/A polymorphism in the gene encoding tumor necrosis factor-α (TNF-α) has been implicated in sepsis risk in many studies but with variable results. The dominant model (AA+GA vs. GG) indicated a significant association between the TNF-α −308 A/G polymorphism and sepsis risk (OR 1.35, 95% CI 1.10–1.67, p = 0.005).[29]

Many studies have assessed that the GA or AA *TNF-α* rs1800629 genotypes were associated with increased sepsis risk.[30] Baghel *et al*. indicated that the TNF-α-308 G/A polymorphism was associated with the development of postoperative sepsis and increased expression of TNF-α, IL-6 and IL-8 genes.[31] Acar *et al*. reported that showed the AA genotype and the A allele of the tumour necrosis factor-alpha (-308 G/A) polymorphism may be used as a predictor of elevated tumour necrosis factor-alpha levels in patients with sepsis.[32]

On the other hand, TNF-α is important for normal body functions, but is also implicated in some disease mechanisms, including sepsis, DM, and cancer.[33-37] There are several known SNPs within the *TNF-α* gene, including rs1800629, rs361525, rs1800630, and others.[38] Associations between *TNF-α* SNPs and sepsis risk are still uncertain. *TNF-α* rs1800629 was reported as a sepsis risk factor in severely injured North Indian patients,[39] critically ill Japanese patients,[40] the Chinese Han population,[41] and Turkish children.[42] However, *TNF-α* rs1800629 was also negatively correlated with sepsis susceptibility in preterm infants in Germany[43] and low-birth-weight infants in Hungary.[44]

The TNF-α - 308A allele was associated with an increased risk for severe sepsis by unadjusted analysis. Patients who were carriers of the A-allele at TNF-α - 308 had a 41% risk (16/39) for severe sepsis versus a 17% risk (20/120) for patients homozygous for the wildtype G-allele (p = 0.002). The unadjusted relative risk for severe sepsis associated with carriage of the TNF-a 2308 A-allele was 3.47 (95% CI 1.56 to 7.73).[13]

Baghel *et al*. suggested that TNF-α-308 G/A polymorphism increased the expression level of TNF-α.[31] With the continuous progression of human genome researches, it is known that different genetics mechanism is the internal material basis of the occurrence and development of many diseases. More and more evidences show that sepsis is affected by multiple gene polymorphisms.[45,46]

The present results of G allele is higher frequency (62.5%) in burn patient with sepsis than A allele (37.5%) agreement with results of other study that showed G allele is higher frequency (127 (88.2%)) in burn patient with sepsis than A allele 17 (11.8%).[32]

CONCLUSION

Sepsis is a medical emergency commonly encountered during the treatment of burn patients. The diagnosis of sepsis following severe burn injury is complex due to similarities in symptoms and clinical manifestations of hypermetabolic reaction to thermal injury and sepsis. The presence of heterozygous GA genotype in the TNF-α-308 was associated with sepsis of burn patient

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