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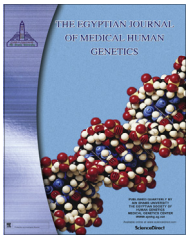

ORIGINAL ARTICLE

The promoter region (G-800A and C-509T) polymorphisms of transforming growth factor-β1 gene among young women with recurrent urinary tract infection

Maimun Syukri [a,*], Mochammad Sja'bani [b], Marsetyawan HNE Soesatyo [c], Indwiani Astuti [d], Imran Imran [e], Harapan Harapan [e,f]

[a] *Department of Internal Medicine, School of Medicine, Syiah Kuala University, Banda Aceh, Indonesia*
[b] *Department of Internal Medicine, Faculty of Medicine, Gadjah Mada University, Yogyakarta, Indonesia*
[c] *Department of Histology and Cell Biology, Faculty of Medicine, Gadjah Mada University, Yogyakarta, Indonesia*
[d] *Department of Pharmacology, Faculty of Medicine, Gadjah Mada University, Yogyakarta, Indonesia*
[e] *Medical Research Unit, School of Medicine, Syiah Kuala University, Banda Aceh, Indonesia*
[f] *Tropical Diseases Centre, School of Medicine, Syiah Kuala University, Banda Aceh, Indonesia*

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Abstract *Background:* Recurrent urinary tract infection (UTI) is common among young women and one of its risk factors is genetic. Polymorphisms in promoter region (G-800A (rs1800468) and C-509T (rs1800469)) of transforming growth factor-β1 (TGF-β1) gene play pivotal roles in several infection diseases but the association of these polymorphisms with recurrent UTI remains unclear. The aim of this study was to assess the correlation of TGF-β1 G-800A and C-509T polymorphisms with recurrent UTI in young women.

Subjects and methods: TGF-β1 G-800A and C-509T polymorphisms among 34 recurrent UTI patients and 34 healthy subjects, aged 15–50 years old, were evaluated with polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and confirmed by DNA sequencing.

Results: At position −800, genotypes showed no significant differences between recurrent UTI patients (GG 97.1%; GA 2.9%; AA 0%) and normal control (GG 97%; GA 0%; AA 2.9%) young

* Corresponding author. at: Department of Internal Medicine, School of Medicine, Syiah Kuala University, Banda Aceh, Indonesia. Tel.: +62 0811685945.
E-mail address: maimun_62@yahoo.com (M. Syukri).

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women. Dominant and recessive model analyses did not find significant correlation between recurrent UTI patients and normal control young women. At position −509, allelic and genotypic frequencies showed no significant differences between recurrent UTI patients (CC 20.6%; CT 61.8%; TT 17.7%) and control individuals (CC 2.9%; CT 73.6%; TT 23.5%).

Conclusion: This study found that there is no strong correlation between polymorphisms of TGF-β1 G-800A and C-509T and recurrent UTI.

1. Introduction

Recurrent urinary tract infection (UTI) is an episode of UTI which is at least two times in six months or three or more re-infections with clinical symptoms of UTI in a year. It is common among young women even with normal urinary tract health. Recurrent UTI is one of the main causes of renal scars, increased renal insufficiency and hypertension, and contributes to high morbidity and increased health care costs [1]. Some hypotheses suggest that recurrent UTI is related with host factors and behavioral risk factors [1,2]. Previous studies found that sexual activity, use of contraception (diaphragm and spermicidal), antibiotics, estrogen, a short anatomical distance between the urethra and anus, and genetic factors were correlated with recurrent UTI [3,4].

Transforming growth factor-β1 (TGF-β1) is a key cytokine that initiates and terminates tissue repair. TGF-β1 is the major fibrogenic growth factor implicated in the pathogenesis of renal scarring [5] and a key mediator of glomerular and tubulo-interstitial pathobiology in chronic kidney diseases [6]. Previous studies have found that TGF-β1 plays a pivotal role in pathogenesis of fibrosis in human kidney [7,8] and glomerular disease [7].

TGF-β1 gene, which is located on chromosome 19q13 and encoded by seven exons [9], has been implicated as a candidate gene in the pathomechanism of numerous kidney diseases. Since TGF-β1 acts as a proinflammatory or anti-inflammatory cytokine depending on its concentration, polymorphisms which alter TGF-β1 production are implicated in numerous diseases [10–15]. Several polymorphisms have been found in the TGF-β1 gene, C-988A, G-800A, C-509T, G-25C, T-10C, G915C, T869C and C788T [10,14,16], and two of the most studied intensively are G-800A and C-509T which are localized in the promoter region. A case-control study reported that TGF-β1 G800A and C-509T polymorphisms are related to renal parenchymal scarring in childhood UTI [11]. Another case-control study found an increase in TGF-β1–800GG and –509CC genotypes among childhood UTI and vesicoureteral reflux (VUR) [12]. However, the role of these polymorphisms in recurrent UTI among young women is still unknown. This study aimed to determine the correlation between TGF-β1 G-800A and C-509T polymorphisms and recurrent UTI among young women.

2. Subjects and methods

2.1. Subjects

Thirty-four young women, aged 15–50 years old, with recurrent UTI which confirmed with clinical manifestation and urine culture and 34 normal young women were included in this study. Recurrent UTI criteria based on Society of Obstetricians and Gynecologists of Canada [17] and European Association of Urology [18] were applied in this study. Normal woman was defined as person with no clinical symptom of UTI in the last three years with no sign and symptom of infection at the enrollment time of this study. Patients post menopause, post manipulated bladder, diabetes mellitus, liver cirrhosis, immunosuppressive diseases, use of immunosuppressive drug, and kidney transplant were excluded from the study. This study was conducted with the approval of the Ethics Committee of School of Medicine, Syiah Kuala University, Banda Aceh, Indonesia, No. 066/KI/FK/201. The subject recruitment and sample collection were done only after obtaining written informed consent of the participants. The work is carried out in accordance with The Code of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

2.2. DNA extraction and TGF-β1 genotyping

DNA isolation was carried out in Molecular Biology Laboratory, School of Medicine, Syiah Kuala University, Banda Aceh, Indonesia; PCR-RFLP was conducted in Faculty of Medicine, Gadjah Mada University, Yogyakarta, Indonesia and DNA sequencing confirmation was conducted in 1st BASE Pte Ltd Laboratory Singapore. Briefly, 2.5 ml peripheral venous blood was obtained from recurrent UTI young women cases and healthy woman, then DNA was extracted from whole blood as described previously [19]. Genotyping was carried out as described in previous report [12]. PCR amplification for each TGF-β1 G-800A and C-509T polymorphism was performed in a total reaction volume of 20 μL with 2 μL of genomic DNA, 5 μL of each of primer, 250 μM dNTP, 40 mM KCl, 1.5 mM $MgCl_2$, 10 1 U *Taq*DNA polymerase and 10 mM Tris–HCl (pH 9.0) (Pharmasia). PCR conditions included denaturation at 94 °C for 5 min, followed by 32 or 35 cycles at 94 °C for 1 min, annealing at 57.5–62 °C for 30–40 s, extension at 72 °C for 1 min, and final extension at 72 °C for 5 min.

For the G-800A polymorphism, 5′-ACAGTTGGCACGG GCTTTCG-3′ was used as forward primer and 5′-TCAACAC CCTGCGACCCCAT-3′ was used as reverse primer. For the C-509T polymorphism, 5′-CCCGGCTCCATTTCCAGGTG-3′ was used as forward primer and 5′-GGTCACCAGAG AAAGAGGAC-3′ was used as reverse primer. Restriction fragment length polymorphism (RFLP) was performed by digestion of 10 μL of PCR product with 10 μL of restriction enzyme for 1 h. For C-509T polymorphism, the PCR products, 808 bp in length, were digested with Bsu36I and for G-800A polymorphism, the PCR products, 388 bp in length, were digested with MaeIII. Digested products were electrophoresed

through ethidium bromide-stained 3% agarose gels. The amplified products, three samples from each group, were confirmed by DNA sequencing, using an ABI PRISM BigDye Terminator Cycle Sequencing Ready Reaction Kit and a 3730 DNA analyzer (Applied Biosystems).

2.3. Statistical analysis

Differences in the genotype, dominant and recessive model, and allele frequencies between recurrent UTI cases and controls were analyzed with Chi-square test to assess the risk of TGF-β1 G-800A and C-509T polymorphisms with recurrent UTI. Genotype data were compared using 2×3 contingency table of Chi-square test, dominant and recessive model, and allele data compared using 2×2 contingency table of Fisher's exact test using statistical computational tools available at http://www.vassarstats.net. Two sided testing was used for all significant comparisons to evaluate statistically a p-value of $\leqslant 0.05$ as significant. Risk factors and recurrent UTI correlations were analyzed with Chi-square test and Fisher's exact test or t-test as appropriate with data.

3. Results

3.1. Sample characteristic and risk factors

A total of 68 young women participants, (34 patients with recurrent UTI, mean age was 32 years old; 34 healthy women as control, mean age was 26.1 years old) were enrolled in this study. Several risk factors of recurrent UTI are presented in Table 1. Age, sexual intercourse frequency (per week), marital status and intrauterine device contraception were significantly correlated with recurrent UTI.

3.2. Polymorphism of TGF-β1 G-800A and C-509T

The location of G-800A and C-509T polymorphisms in the TGF-β1 promoter (modified from [20]), and the electrophoresis results of PCR-RFLP are shown in Fig. 1. For the G-800A polymorphism genotyping, the PCR products, 388 bp in length, were digested with *Mae*III. Two fragments of 205 and 183 bp are categorized as homozygous GG genotype, whereas a 388 bp fragment was categorized as homozygous AA genotype. Three fragments of 388, 205 and 183 bp were categorized as heterozygous GA (Fig. 1B). For the C-509T polymorphism genotyping, the amplified 808 bp fragments were digested with *Bsu*36I. Two fragments of 617 and 191 bp were shown if the product was digestible and categorized as homozygous CC genotype (cuttable), whereas 808 bp fragment was categorized as homozygous TT genotype (uncuttable). Three fragments of 808, 617 and 191 bp were categorized as the heterozygous CT genotype (Fig. 1C).

In this study, 97.1% (33 of 34 subjects in both the recurrent UTI and control groups) were homozygous GG at G-800A. Only a single subject with recurrent UTI (2.9%) had the heterozygous GA genotype. Only one of the normal subjects was found to have the homozygous genotype AA (Table 2). There was no statistically significant difference in G-800A genotype or allele frequencies between recurrent UTI young women and controls. Evaluation of C-509T genotypes indicated that 7 (20.6%) of recurrent UTI and 1 (2.9%) of normal subjects, have the CC genotype. In addition, 21 (61.8%) of the recurrent UTI and 27 (73.6%) of normal subjects were the heterozygous CT genotype. The TT genotype was found in 6 (17.7%) of recurrent UTI cases and 8 (23.5%) of normal subjects (Table 2). After adjustment, there was no statistically significant difference in C-509T genotype or allele frequency distributions between recurrent UTI young women and controls; however, there is a significant association between recurrent UTI in young women and the C-509T locus C allele when considering a genetic dominance model.

4. Discussion

There are several risk factors of recurrent UTI such as frequent sexual intercourse, use of contraception (intrauterine device contraception, diaphragm and spermicidal), use of antibiotics, UTI history, and mother with UTI history, estrogen levels, and anal and urethra anatomy [2,3,21–23]. Our results support previous findings of sexual intercourse frequency, marital status and intrauterine device contraception that were correlated with recurrent UTI.

Besides those risk factors, various studies have been conducted to investigate genetic factors of recurrent UTI susceptibility in humans. A review study found that several genes in humans such as CXCR1, CXCR1, TLR2, TLR4, HSPA1B and TGF-β1 were associated with susceptibility to recurrent UTI [13]. The role of TGF-β1 in recurrent UTI has not been studied. TGF-β1 is an important immunoregulatory cytokine, it controls cell proliferation, synthesizes extracellular matrix, and plays a pivotal role in cellular immunity response. It

Table 1 Risk factors of recurrent UTI.

Risk factors		Subjects		OR (95% CI)	p
		R-UTI	Control		
Married*	Yes	29	10	13.9 (4.2–46.3)	0.000
	No	5	24		
Intrauterine device*	Yes	7	1	8.6 (0.9–73.9)	0.027
	No	27	33		
Age (years)†		32	26.1		0.000
Sexual intercourse frequency (per week)†		1.9	0.62		0.000

R-UTI, recurrent urinary tract infection; OR, odd ratio. 95% CI, 95 confidence interval.
* Analyzed with Chi-square or Fisher's exact test.
† Analyzed with t-test.

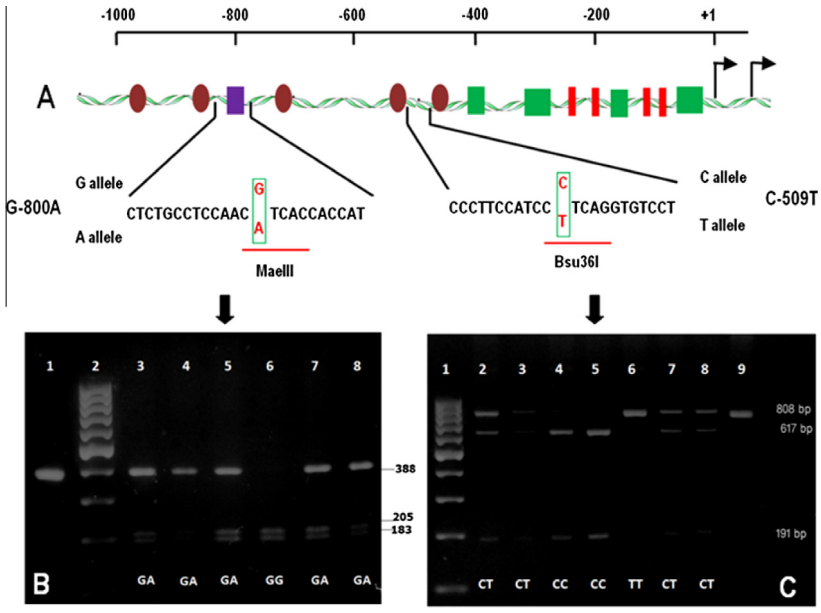

Figure 1 Location of G-800A and C-509T polymorphisms in the TGF-β1 promoter and electrophoresis pattern of polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) of these polymorphisms. (A) Diagrammatic representation of the putative transcription factor binding sites in the TGF-β1 promoter and restriction site of MaeIII and Bsu36I (modified from [20]). (B and C) Electrophoresis pattern of PCR-RFLP G-800A and C-509T polymorphisms. Green boxes are sp1 transcription factor binding sites; vertical red lines are activating protein 2 (ap2) transcription factor binding site; brown ovals are nuclear hormone binding element; purple box is cAMP response element-binding (CREB) half-site.

Table 2 Distribution of allelic and genotypic of the TGF-β1 in recurrent UTI (N = 34) and control groups (N = 34).

TGF-β1 genotype and allele	R-UTI N (%)	Control N (%)	p	OR (95% CI)
Genotype: C-509T				
CC	7 (20.6)	1 (2.9)		
CT	21 (61.8)	25 (73.6)		
TT	6 (17.7)	8 (23.5)	0.077	
Dominant model				
CC	7 (20.6)	1 (2.9)		
CT + TT	27 (79.4)	33 (97.1)	0.054	0.12 (0.01–1.01)
Recessive model				
CC + CT	28 (82.4)	26 (76.5)		
TT	6 (17.6)	8 (23.5)	0.765	0.69 (0.21–2.28)
Allele				
C	35 (51.5)	27 (39.7)		
T	33 (48.5)	41 (60.3)	0.220	0.62 (0.31–1.22)
Genotype: G-800A				
GG	33 (97.1)	33 (97.1)		
GA	1 (2.9)	0 (0.0)		
AA	0 (0)	1 (2.9)	0.368	-
Dominant model				
GG	33 (97.1)	33 (97.1)		
GA + AA	1 (2.9)	1 (2.9)	1.000	1 (0.06–16.66)
Recessive model				
GG + GA	34 (100)	33 (97.1)		
AA	0 (0.0)	1 (2.9)	0.999	0 (0-NaN)
Allele				
G	67 (98.5)	66 (97.1)		
A	1 (1.5)	2 (2.9)	0.999	0.49 (0.04–5.56)

R-UTI, recurrent urinary tract infection; OR, odd ratio. 95% CI, 95 confidence interval.

inhibits proliferation of T and B cells, antagonizes proinflammatory cytokines (TNF-α and IFN-γ), blocks cytotoxic T lymphocyte activity and inhibits induction of receptors for IL-1 and IL-2, inhibits adhesion of T cells and neutrophils to endothelial cells, inhibits activation of macrophages and down regulates MHC class II expression on macrophages [24]. Because of these activities, a number of reports found that TGF-β1 has multiple roles to play in the pathogenesis of several infectious diseases (both non-urinary tract infection and urinary tract infection) and immunologic diseases [11–15,25–32]. TGF-β1 polymorphism is correlated with UTI in children and vesicoureteral reflux [11,12], dengue infection [10], hepatitis C infection [13], and the development of chronic periodontitis [14]. The level of TGF-β1 is correlated with HIV infection [25], hepatitis B infection [26], influenza A H1N1 [27] and some parasitic infections such as *Trypanosoma cruzi* [28] and *Plasmodium yoelii* [29]. In addition, TGF-β1 is also associated with immunologic diseases such as systemic sclerosis [30], rheumatoid arthritis [31], and psoriasis vulgaris [32]. Previous research aimed to measure the TGF-β1 level in urine as a response marker towards immunosuppressive treatment in crescentic nephritis found that TGF-β1 concentration in urine was elevated significantly in patients without improving kidney function with immunosuppressive treatment [33]. A couple of studies implicated that TGF-β1 plays a pivotal role in congenital obstructive uropathy pathogenesis and acute pyelonephritis [12,34]. A case control study in pediatric patient with chronic kidney disease reported that TGF-β1 excretion was higher compared with TGF-β1 levels in healthy children [34]. TGF-β1 also has a pivotal role in glomerular filtration barrier loss and proteinuria [35]. TGF-β1 is involved in extracellular matrix accumulation, fibrosis, renal impairment progression, changes to the glomerular filtration barrier, induction of proteinuria [35], associated with IgA nephropathy and thin glomerular basement membrane disease [36]. TGF-β1 overexpression has caused proteinuria in animal models [37] and inhibition of TGF-β1 reduces proteinuria [38].

Nine polymorphisms have been identified in the TGF-β1 gene: three reside in the promoter region, C-988A, G-800A, C-509T, an insertion (C) in the 5′UTR at position +72, two polymorphisms are in the signal sequence, one in exon 5 and one in each of introns 4 and 5 [39]. G-800A polymorphism is in a consensus cAMP response element-binding (CREB) half-site and the A allele would be expected to have reduced affinity for the CREB family of transcription factors, consequently contributing to a lower production of total TGF-β1 in the circulation [20,40]. In addition, the −509T allele had previously been associated with higher serum concentration of TGF-β1 [38]. The association of TGF-β1 G-800A and C-509T polymorphisms with several diseases related to urinary tract infection has been investigated in a couple of studies [11,12]. A case-control study reported that TGF-β1 G-800A and C-509T polymorphisms were linked to kidney parenchymal scarring in childhood after UTI [11]. TGF-β1 genotypes were associated with an alteration of the host response to UTI in children [12]. Yim et al. [12] found that an increased −509CC and −800GG genotype frequency and decreased −509TT and −800GA genotype frequency were related to UTI.

Recurrent UTI may result from defect of local defense. This might be explained by opsonizing antibody weakness, which leaves the urinary tract mucous unable to neutralize microbial invasion. This explanation is supported with the unique bladders mucous because of opsonizing antibody weakness impacts; therefore, urinary tract mucous become unable to neutralize the microorganisms invasion. Other factors, such as weakening of host immunity, also lead to recurrent UTI [1]. Because TGF-β1 has important roles in human immunity system, as mentioned before, various studies found that TGF-β1 polymorphisms were associated with several infectious [10,13,14] and immunologic diseases [30–32]. All of those data reveal that TGF-β1 has a pivotal role in infection and immunologic-diseases. However, this study found there was no significant association between TGF-β1G-800A and T-509C polymorphisms and recurrent UTI. Yim et al. [12] also state that it is difficult to determine whether the TGF-β1 polymorphisms correlate with risk of UTI.

There are some limitations of this study. First, the sample size of the phenotype groups was relatively small. Second, serum TGF-β1 concentrations or gene expression of TGF-β1 in peripheral blood mononuclear cells were not measured. The TGF-β1 concentrations are important because although several studies found that G-800 and T-509 alleles are associated with serum or *in vitro* TGF-β1 level; contrasting results have been published [11,20,41]. Therefore, further study comparing TGF-β1 gene polymorphisms, measuring transcription and TGF-β1 concentrations in serum with large sample size is required to investigate the potential roles of TGF-β1 on recurrent UTI.

5. Conclusion

In conclusion, there was no strong association between two TGF-β1 genetic variants' promoter region (positions: −800 and −509) with recurrent UTI among young women.

Disclosure statement

There is no conflict of interest in this study.

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