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Original Research Article

There is no correlation between the functional polymorphism −460C>T of vascular endothelial growth factor (VEGF) gene promoter and uncomplicated recurrent urinary tract infection among young women

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ABSTRACT

Introduction: The −460C>T polymorphism in vascular endothelial growth factor (VEGF) gene promoter (rs833061) has robust association with various diseases including renal parenchymal scarring following urinary tract infection (UTI). However, the association of this polymorphism with uncomplicated recurrent UTI (RUTI) is still unclear.

Aim: The objective of this study was to assess the correlation between VEGF −460C>T polymorphism and uncomplicated RUTI among young women.

Material and methods: Polymerase chain reaction – restriction fragment length polymorphism (PCR-RFLP) with *Bst*U1 restriction enzyme – and DNA sequencing were used to determine the VEGF −460C>T polymorphism among 34 young adult women with uncomplicated RUTI and 34 healthy controls. Differences in genotype and allele frequencies between case and control groups were analyzed with χ^2 test or Fisher's exact test.

Results and discussion: This study found that there was no significant difference in genotype frequencies between cases (CC 23.5%; CT 26.5%; TT 0%) and controls (CC 85.3%; CT 14.7%; AA 0%). Dominant model analysis found that there was no significant difference between uncomplicated RUTI and normal groups ($P = 0.368$). Similarly, allele analysis also found that there was no association between VEGF −460C>T polymorphism and uncomplicated RUTI ($P = 0.398$).

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Conclusions: This study found that there was no correlation between VEGF −460C>T polymorphism and uncomplicated RUTI among young women.

1. Introduction

Recurrent urinary tract infection (RUTI) is an episode of urinary tract infection (UTI) at least two times in six months or three or more re-infections with clinical symptoms in a year. RUTI is one of the major causes of renal scars; it also increases the incidence of renal insufficiency and hypertension, contributes to high morbidity and increases health care costs. Some studies found that RUTI was related to behavioral risk factors (sexual activities, diaphragm and spermicidal use, antibiotics use or estrogen use),[1–3] host factors for instance a short anatomical distance between the urethra and anus,[1,2] and genetic factors such as polymorphisms in several genes that encode cytokines and inflammatory mediators.[4,5]

Vascular endothelial growth factor (VEGF, referred to VEGF-A in this study) is a key mediator of normal and abnormal angiogenesis (proliferation, sprouting, migration and tube formation of endothelial cells) and an important regulator of vascular permeability.[6,7] In addition, several studies found that VEGF is an important molecule in several diseases.[7–11] VEGF belongs to VEGF family that includes VEGF-B, VEGF-C, VEGF-D and placenta growth factor (PlGF).[6] Because VEGF has pivotal roles in endothelial cells – an important medium of transporting immune system components between blood circulation and epithelial compartment – therefore, it could has important roles in infection including UTI.

VEGF gene, located on chromosome 6 at 6p21.3, is organized in 8 exons separated by 7 introns and the coding region encompasses approximately 14 kb.[12] VEGF gene is highly polymorphic and numerous single nucleotide polymorphisms (SNPs) can be found in the promoter and 5′ untranslated region (5′-UTR).[13,14] Common SNPs in VEGF gene have been studied and one of the most consistent SNP with several diseases is VEGF −460C>T. Study found that the person with VEGF −460C allele had higher VEGF protein expression[15] and VEGF −460C>T polymorphism had strong correlation with susceptibility, development, progressivity and prognosis of several diseases.[16–22]

Focusing on urinary tract diseases, a previous study revealed that VEGF −460C>T polymorphism is related to renal parenchymal scarring in childhood UTI.[23] Another study found that UTI cases (with or without vesicoureteral reflux (VUR) complication) had association with VEGF −460C>T polymorphism.[24] However, there was no association of this polymorphism with uncomplicated-UTI.[24] Another study also found similar findings.[25] They found that VEGF −460 CC genotype was more frequent in UTI with VUR complication cases compared to healthy controls or UTI without VUR complication cases. However, the role of this polymorphism in uncomplicated RUTI is still unknown.

2. Aim

The objective of this present study was to determine the correlation between VEGF −460C>T polymorphism and uncomplicated RUTI among young women.

3. Material and methods

3.1. *Subjects*

This case–control study was conducted with 34 culture-confirmed uncomplicated RUTI cases in young women (age range was 15–50 years old) and 34 normal women. Uncomplicated RUTI criteria that were applied in this study have been published previously.[26] Uncomplicated RUTI criteria in this study were: (a) UTI that occurred three times or more in 12 months or two times or more in 6 months; (b) no structural and functional abnormality of the urinary tract (based on standard blood urea nitrogen and creatinine analysis and sonography); (c) mid-stream sample of urine $<10^3$ cfu/mL of uropathogen; and (d) infection was confirmed with mid-stream urine culture. All complicated RUTI cases were excluded from this study. In addition, several exclusion criteria such as post-menopause, post-manipulated bladder, diabetes mellitus, liver cirrhosis, immunosuppressive diseases, use of immunosuppressive drug, and kidney transplant were applied to potential subjects. As control, a group of young women (doctors, nurses and medical students) who were free of the clinical symptom of UTI in the last 3 years and had no sign and symptom of infection was recruited. The subject recruitment and sample collection were conducted only after obtaining written informed consent of the participants. The work was carried out in accordance with The Code of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

3.2. *Deoxyribonucleic acid (DNA) extraction*

For DNA extraction purpose, 2.5 mL peripheral venous blood was collected from 68 subjects (34 cases and 34 controls) and DNA was extracted from whole blood using the salting-out method as described previously.[27]

3.3. *SNP genotyping*

Genotyping was carried out as described in a previous report.[24] Briefly, to amplify VEGF gene, forward primer: