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Associations of *VEGF* Gene Polymorphisms With Erectile Dysfunction and Related Risk Factors

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ABSTRACT

Background: Repeated evidence from animal models suggests a strong link between vascular endothelial growth factor (VGEF) and penile vasculature and erectile function because VEGF can alter the physiologic pathways involved in the regulation of penile vasomotor tone.

Aim: To investigate three VEGF polymorphisms and their link to erectile dysfunction (ED).

Methods: We enrolled 688 Taiwanese men with a mean age of 55.6 years (SD = 4.5) during a free health screening. All participants provided complete medical histories and underwent physical examinations. Fasting blood samples were obtained for biochemical analysis and hormone profiling. The allelic discrimination of three *VEGF* gene polymorphisms (460T/C [rs833061], 1154G/A [rs1570360], and 2578A/C [rs699947]) was performed using validated TaqMan single-nucleotide polymorphism genotyping assays.

Outcomes: Subjects underwent assessment using the simplified five-item International Index of Erectile Function to diagnose and assess ED severity.

Results: The results showed that diabetes mellitus (odds ratio [OR] = 3.27, $P < .01$), hypertension (OR = 3.47, $P < .01$), and having the *VEGF* 2578A allele (OR = 1.54, $P = .01$) were the three most independent risk factors for ED. In univariate analysis, all three *VEGF* polymorphisms (460C, 1154A, and 2578A) were significantly associated with a higher prevalence of coronary artery disease ($P < .01$) and greater frequencies of hypertension were found in carriers of the 1154A allele and the 2578A allele ($P = .01$). Multiple logistic regression analysis showed a significant association between *VEGF* 2578A allele carrier status and ED (OR = 1.54, 95% CI = 1.10∼2.15, $P = .01$). Furthermore, the prevalence and severity of ED were significantly increased with an increment of the 2578A allele number ($P < .05$).

Clinical Implications: *VEGF* 2578C/A gene polymorphisms could be a genetic susceptibility factor for the development of ED.

Strength and Limitation: This is the first study to investigate the genetic susceptibility of *VEGF* polymorphisms to ED. This study was cross-sectional with a lack of functional and molecular production investigations. Data on the association among conditions might not allow definitive conclusions about causal links.

Conclusion: This study showed that *VEGF* 2578A allele carriers in a Taiwanese population are at greater risk for ED. **Lee Y-C, Huang S-P, Tsai C-C, et al. Associations of *VEGF* Gene Polymorphisms With Erectile Dysfunction and Related Risk Factors. J Sex Med 2017;14:510–517.**

Key Words: Vascular Endothelial Growth Factor; Gene Polymorphisms; Erectile Dysfunction; Risk Factors

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INTRODUCTION

Erectile dysfunction (ED) is estimated to affect 52% of men, with the highest prevalence in men 40 to 70 years old.[1] Until the 1980s ED was considered primarily a psychogenic disease. Since then, extensive research efforts have proved that ED is caused by an organic disease in up to 80% of cases. Of the organic ED cases, 40% involved vascular problems that can be largely caused by endothelial dysfunction.[2] Indeed, ED and systemic vascular diseases share many common risk factors. A body of literature has identified ED as a marker of silent vascular disease.[3]

Vascular endothelial growth factor (VEGF) is a multifunctional glycoprotein secreted in the vascular wall by endothelial and smooth muscle cells.[4] VEGF can induce receptor-mediated endothelial proliferation in vitro and in vivo and is known to be a potent vasculogenic and vascular permeability factor related to endothelial function.[5] Particularly important for the diseased corpus cavernosum, repeated evidence from animal models has suggested a strong link between VEGF and its influence on penile vasculature and erectile function, because it can alter physiologic pathways involved in the regulation of penile vasomotor tone. The therapeutic uses of VEGF have been successfully demonstrated in these animal models.[6–8] In addition, the nitric oxide (NO) pathway is of critical importance in the physiologic induction and maintenance of erections.[9] Recent studies have demonstrated that VEGF can stimulate endogenous NO production, exerting positive effects on endothelial and smooth muscle cells and thus improving erectile function.[10,11]

The human gene encoding VEGF is located on chromosome 6p21.3 and is composed of eight exons and seven introns, with an overall length of approximately 14 kb.[12] Several functional single-nucleotide polymorphisms (SNPs) have been described in the *VEGF* gene. Currently, evidence has accumulated proving these polymorphisms, especially on the promoter region, can mediate alterations in VEGF concentrations and are associated with an increased risk of developing cardiovascular disorders. They affect some of those exact same physiologic pathways that are known to play a role in the regulation of penile vasomotor tone.[13,14] Considering the close relation between the pathophysiology of cardiovascular disorders and ED, finding common genetic factors influencing the two disorders seems feasible.

To our knowledge, this is the first study to investigate the genetic susceptibility of *VEGF* polymorphisms to ED. We chose three functional SNPs of the *VEGF* gene on the promoter region (460T/C [rs833061], 1154G/A [rs1570360], and 2578C/A [rs699947]) that have been shown to modify *VEGF* gene promoter activity and therefore affect circulating VEGF levels in vivo.[15,16] The aim of this study was to assess the potential associations of the three *VEGF* gene polymorphisms with ED and related risk factors.

METHODS

All methods were carried out in accordance with relevant guidelines and regulations. All experimental protocols were approved by the institutional review board of the Kaohsiung Medical University Hospital (Kaohsiung, Taiwan) and all subjects provided informed consent before their participation was allowed.

We conducted a population-based study of 688 Taiwanese men. All enrolled subjects were volunteers older than 40 years who underwent a health screening at our institution. The screening was open to the general male population living in the city of Kaohsiung. We took all subjects' complete medical, surgical, and psychosexual histories. Detailed physical examinations, including weight, height, blood pressure, digital rectal examination, and transrectal ultrasonography for prostate volume evaluation, also were performed. Body mass index was calculated as body weight (kilograms) divided by the square of body height (meters). Fasting blood samples were taken for biochemical analysis, hormone profiling, and genetic testing.

The well-known vascular risk factors for ED were completely reviewed. Subjects were defined as alcohol drinkers, cigarette smokers, or betel nut chewers if they regularly consumed any alcoholic beverage at least once per week, smoked at least 10 cigarettes per week, or chewed at least seven betel quids per week, respectively, and had indulged in the habit for at least 6 months before this examination.[17] A history of coronary artery disease (CAD) was defined as having at least one physician diagnosis of acute myocardial infarction or angina with available medical records. Hypertension was defined as a systolic pressure of at least 140 mm Hg or a diastolic pressure of at least 90 mm Hg. Diabetes mellitus (DM) was diagnosed as a fasting blood glucose level of at least 126 mg/dL. Hyperlipidemia was defined as a total cholesterol level of at least 200 mg/dL or a triglyceride level of at least 200 mg/dL.[18] Individuals with a history of hypertension, DM, or hyperlipidemia, but under control by regular medication, were included.

All enrolled subjects had sexual relationships with a regular partner for 6 months before undergoing the health investigation. Patients with ED were defined as those who subjectively had been unable to achieve or maintain an erection sufficient for sexual intercourse. These subjects completed the five-item International Index of Erectile Function (IIEF-5) to confirm the diagnosis of ED and evaluate the severity of their ED according to the IIEF-5 total score. Subjects were diagnosed with ED if they had an IIEF-5 score lower than 22.[19] Severe ED was defined as an IIEF-5 score no higher than 7.[19] Men participating in this health investigation also were asked to complete the International Prostate Symptom Score questionnaire to evaluate lower urinary tract symptoms.

Excluded were patients (i) who had undergone surgical or medical therapy (phosphodiesterase type 5 inhibitors or testosterone replacement) for ED; (ii) who had primary hypoactive sexual desire or ED because of an anatomic penile abnormality; (iii) who had a history of neurologic disease or malignancy; and (iv) who had any medical psychiatric history or substance abuse disorders.