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Meta Analysis

Ethnic differences in the association between angiotensin-converting enzyme gene insertion/deletion polymorphism and peripheral vascular disease: A meta-analysis

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Abstract

Background: Several studies have investigated the association of angiotensin-converting enzyme (*ACE*) gene insertion/deletion (I/D) polymorphism with peripheral vascular disease (PVD); however, the results remain controversial. Therefore, we conducted the current meta-analysis to evaluate this relationship in the general population of different ethnicities.

Methods: We searched PubMed, Embase, Web of Science, Wanfang Database, and CNKI to identify eligible studies. Random-effect models were applied to estimate the pooled odds ratio (*OR*) with a 95% confidence interval (*CI*), regardless of between-study heterogeneity.

Results: A total of 13 studies with 1966 cases and 6129 controls were included in this meta-analysis. The pooled *OR*s for the association between *ACE* I/D polymorphism and PVD risk were not statistically significant in the overall population under all genetic models. In further ethnicity-stratified analyses, we found a statistically significant association of *ACE* I/D polymorphism with PVD susceptibility in Asians under most models. However, the association among Caucasians did not reach statistical significance.

Conclusion: *ACE* I/D polymorphism might be associated with susceptibility to PVD in the Asian population, but there was no clear evidence indicating a similar significant relationship among Caucasians.

Keywords: Peripheral vascular disease; Angiotensin-converting enzyme; Insertion/deletion polymorphism; Meta-analysis

Introduction

Peripheral vascular disease (PVD) is a common manifestation of systemic atherosclerosis, which encompasses numerous noncoronary arterial syndromes. It is associated with an increased risk of cardiovascular events,[1] affecting approximately 20% of adults aged 55 years or older and an estimated 27 million persons in North America and Europe.[2] Apart from traditional

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cardiovascular risk factors, several novel biologic mediators and genetic predisposing factors have been implicated in the atherogenic process leading to PVD.[3−5] PVD is a complex trait influenced by multiple environmental triggers and genetic factors as well as their interactions, which are not yet completely defined.

Many studies have investigated the relevance of polymorphisms in renin angiotensin system (RAS) genes with PVD but reported conflicting results. Among the polymorphisms in RAS candidate genes, the angiotensin-converting enzyme (*ACE*) insertion/deletion (I/D) polymorphism has attracted special attention owing to its functional roles. The *ACE* gene is located on the long arm of chromosome 17 (17q23) in humans and contains 26 exons and 25 introns. *ACE* I/D polymorphism (dbSNP rs1799752, chromosome position 63,488,529 GRCh37) results from the presence or absence of a 287-bp Alu repeat in intron 16 of the *ACE* gene.[6] The population minor allele frequency (MAF) of this SNP is lower than 0.01. The *ACE* I/D polymorphism is known to be responsible for nearly half of the total phenotypic variance of circulating, intracellular, and tissue *ACE* in Caucasians, with higher serum *ACE* level and activity in D allele carriers.[7,8]

ACE, a key component of the RAS system, hydrolyzes angiotensin I to the potent vasoconstrictor and aldosterone-stimulating peptide angiotensin Ⅱ, and inactivates the vasodilator bradykinin. This biological process results in decreased tissue perfusion, vascular smooth muscle cell growth, and stimulation of plasminogen-activator inhibitor type I.[9,10] Chronic exposure to high levels of circulating and tissue *ACE* may also lead to vascular wall thickening and atherosclerosis.[3] Thus, those who carry a susceptible gene polymorphism of *ACE* may experience chronically unbalanced vasoconstriction and vasorelaxation. The unbalanced vascular tones subsequently increase arterial stiffness, ultimately predisposing them to lower extremity arterial disease (LEAD) or other vascular diseases.[5]

There is mounting evidence proving the vital role of the D allele of the *ACE* gene in various cardiovascular diseases among different populations. Many studies supported the hypothesis that the *ACE* D allele confers an increased risk of vasculitis, especially in Behcet's disease and Henoch-Schönlein purpura.[11,12] The DD genotype and D allele were also found to be strongly associated with hypertension in different populations.[13,14] Moreover, cumulative evidence has confirmed the effect of *ACE* I/D polymorphism on the onset of type 2 diabetes mellitus (T2DM).[15,16] Given the importance of the *ACE* gene in the pathogenesis of hypertension, T2DM, vasculitis, and other predisposing causes to PVD,[17] it is biologically plausible that these variants modulate the risk of PVD. Moreover, PVD *per se* is an atherosclerotic process.[18] Thus, the *ACE* gene may be a good candidate gene for PVD study.

Although multiple studies have attempted to link *ACE* I/D polymorphism to PVD, the results remain controversial.[4,5,19−28] This lack of reproducibility might stem from methodological limitations of the available studies, including insufficient sample size, different definitions of PVD, ethnic heterogeneity, conceivable selection bias, environmental factors, as well as true variability between populations.[29] Therefore, we conducted a meta-analysis to derive a more precise estimation of the association between *ACE* I/D polymorphism and PVD risk.

Methods

Search strategy

The PubMed, Embase, Web of Science, Wanfang Database, and CNKI were searched for relevant studies published before July 2016 using the following searching strategy: “peripheral artery disease” OR “peripheral arterial disease” OR “peripheral vascular disease” OR “peripheral vascular occlusive disease” OR “peripheral arterial occlusive disease” OR “lower extremity arterial disease” OR “intermittent claudication” OR “limb ischemia” OR “atherosclerotic vascular disease” OR “PVD” OR “PAD” OR “PVOD” OR “PAOD” OR “LEAD”) AND (“*ACE*” OR “angiotensin converting enzyme”) AND (“gene” OR “genotype” OR “gene variant” OR “polymorphism” OR “gene polymorphism” OR “SNP”). Bibliographies in the published articles provided further references. Following this search, we also searched the reference list to identify potentially relevant articles. Studies with the most complete data were included when there were multiple publications based on overlapping data.

Inclusion and exclusion criteria

The titles, abstracts, and full texts were reviewed. In this article, we mainly focused on lower-extremity peripheral artery disease (PAD), a chronic occlusive disease of aortic, iliac, and lower-limb arteries.[30] Thus, cases were considered to be patients suffering from lower-extremity PAD, with the diagnosis based on both noninvasive and invasive diagnostic tools. Eligible studies fulfilled the following inclusion criteria: 1)

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