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Endothelial nitric oxide synthase (eNOS) 4b/a polymorphism and the risk of diabetic nephropathy in type 2 diabetes mellitus: A meta-analysis ☆

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ABSTRACT

Many studies have accessed the association between eNOS-4b/a polymorphism and the risk of diabetic nephropathy (DN) among type 2 diabetic subjects. However, the results are conflicting and inconclusive. The aim of current meta-analysis was to more precisely estimate the relationship. Pubmed, Embase, the China National Knowledge Infrastructure and the Wanfang Database were searched for articles published up to May 26th, 2013 that addressed eNOS-4b/a polymorphism and the risk of DN among type 2 diabetic subjects. 18 studies were included in this meta-analysis. eNOS-4b/a polymorphisms were associated with an overall significantly increased risk of DN (allele model: OR = 1.44, 95% CI = 1.14–1.82; additive model: OR = 2.03, 95% CI = 1.14–3.62; dominant model: OR = 1.34, 95% CI = 1.07–1.68; recessive model: OR = 2.01, 95% CI = 1.12–3.61). Subgroup analysis revealed a significant association between the eNOS-4b/a polymorphism and DN in Asian population, especially in Chinese population, but not in non Asian populations. Our meta-analysis supported an association between the 4b/a polymorphism of eNOS gene and increased risk of DN in type 2 diabetes among Asians, especially in Chinese population.

Abbreviations: eNOS, endothelial nitric oxide synthase; DN, diabetic nephropathy; ESRD, end-stage renal disease; ACE, angiotensin-converting enzyme; MTHFR, methylenetetrahydrofolate reductase; CNKI, China National Knowledge Infrastructure; OR, odds ratio; CI, confidence interval; HWE, Hardy–Weinberg equilibrium; FEM, fixed-effects model; REM, random-effects model.

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Introduction

Diabetic nephropathy (DN) is one of the most serious microvascular complications of diabetes and is the leading cause of end-stage renal disease (ESRD) globally (Collins et al., 2012; Liao, 2012). It has become the primary diagnosis in almost 50% of patients starting renal replacement therapy in some Asian countries (Tang, 2010), in Europe and in the US. Asians, including Chinese type 2 diabetic subjects, have a higher prevalence of nephropathy, with 20% having clinical proteinuria and 40% microalbuminuria (Wu et al., 2005).

Why some type 2 diabetics develop nephropathy, whereas others do not, despite having a long-term hyperglycemia remains unknown. Accumulated evidences suggest that both environmental and genetic factors are related with the etiology of DN (Adler et al., 2003; McCarthy, 2010; Stanton and King, 2011). A number of genes have been suggested as diabetic nephropathy candidate genes, for example, angiotensin-converting enzyme (ACE) (Wang et al., 2012), eNOS, methylenetetrahydrofolate reductase (MTHFR) (Yang et al., 2013), among which eNOS may play a critical role because endothelial dysfunction is considered as an important pathophysiologic factor for DN (Futrakul et al., 2006).

Nitric oxide (NO), a vasodilator molecule, is produced through the oxidation of L-arginine by eNOS (Moncada and Higgs, 1993). NO can regulate endothelial function and is an important factor in the maintenance of homeostasis. The presence of eNOS polymorphisms might contribute to a decreased eNOS activity and a reduced NO level, and has been reported to be a potential factor in the pathogenesis and development of DN (Ahluwalia et al., 2008; Palm et al., 2009). This polymorphism consists of the two alleles of eNOS 4a with 4 tandem 27-repeats and eNOS 4b with 5 repeats (Bellini et al., 2007).

To date, many studies have been carried out to investigate the relationship between eNOS-4b/a polymorphism and the risk of DN among type 2 diabetic subjects, but results of these studies were conflicting and inconclusive. Some studies observed that there was an association between eNOS-4b/a polymorphism and the risk of DN in patients with type 2 diabetes (Ahluwalia et al., 2008); while others suggested that there was no significant association (Fujita et al., 2000; Shoukry et al., 2012). To draw a more reliable conclusion, we performed a meta-analysis of all available studies dealing with the relationship between the eNOS-4b/a polymorphism and DN among type 2 diabetic subjects. Subgroup analyses were performed according to different geographic location to investigate ethnicity-specific effects.

Materials and methods

Literature search strategy

Two investigators (ZJM and HZR) independently searched Pubmed, Embase, the China National Knowledge Infrastructure (CNKI) database and the Wanfang Database. The last updated search was performed on May 26th, 2013. We used any possible combinations of relevant keywords of "Endothelial nitric oxide synthase", "eNOS", "4b/a", "polymorphism" and each term designating "T2DM-DN" (e.g., "type 2 diabetes", "T2D", "nephropathy", "albuminuria", "proteinuria", and "ESRD"). We also reviewed all the references cited in these articles to identify additional relevant publications. There was no language limitation. For overlapping publications, only the most recent or complete study was included in this meta-analysis.

Inclusion and exclusion criteria

All studies included in the meta-analysis were required to meet the following criteria: (1) case–control, (2) studies investigating the association of eNOS-4b/a polymorphism with T2DM-DN as the outcome, (3) the control group with subjects who had T2DM but were free of diabetic kidney disease, (4) available data to estimate an odds ratio (OR) with 95% confidence interval (CI),and (5) genotype distribution among the control group must be in Hardy–Weinberg equilibrium (HWE).

Studies were excluded if one of the following existed: (1) review articles and editorials; (2) case reports; (3) repeat or overlapping publications; (4) no report about the genotype frequency, or insufficient information for data extraction.