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ACE insertion/deletion (I/D) polymorphism and diabetic nephropathy

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ABSTRACT

Context: Angiotensin converting enzyme (ACE) gene encodes ACE, a key component of renin angiotensin system (RAS), plays an important role in blood pressure homeostasis by generating the vasoconstrictor peptide angiotensin II.
Evidence Acquisitions: Directory of Open Access Journals (DOAJ), Google Scholar, Pubmed (NLM), LISTA (EBSCO) and Web of Science have been searched.
Results: The presence of ACE insertion/deletion (I/D) polymorphism affects the plasma level of ACE. ACE DD genotype is associated with the highest systemic and renal ACE levels compared with the lowest ACE activity in carriers of II genotype.
Conclusions: In this review focus has been performed on the study of ACE I/D polymorphism in various populations and its influence on the risk of onset and progression of diabetic nephropathy. Also, association between ACE I/D polymorphism and response to ACE inhibitor and angiotensin II receptor antagonists will be reviewed. Further, synergistic effect of this polymorphism and variants of some genes on the risk of development of diabetic nephropathy will be discussed.

Review Article

Implication for health policy/practice/research/medical education:
The presence of angiotensin converting enzyme (ACE) insertion/deletion (I/D) polymorphism affects the plasma level of ACE. ACE DD genotype is associated with highest systemic and renal ACE levels, compared with the lowest ACE activity in carriers of II genotype. Most studies confirmed that ACE I/D polymorphism is involved in the susceptibility to overt nephropathy with protective role of ACE II genotype against the disease in both type 1 and 2 diabetes mellitus. In this review focus has been performed on the study of ACE I/D polymorphism in various populations and its influence on the risk of onset and progression of diabetic nephropathy.

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1. Context

The presence of angiotensin converting enzyme (ACE) insertion/deletion (I/D) polymorphism affects the plasma level of ACE. ACE DD genotype is associated with highest systemic and renal ACE levels, compared with the lowest ACE activity in carriers of II genotype. Most studies confirmed that ACE I/D polymorphism is involved in the susceptibility to overt nephropathy with protective role of ACE II genotype against the disease in both type 1 and 2 diabetes mellitus. In this review focus has been performed on the study of ACE I/D polymorphism in various populations and its influence on the risk of onset and progression of diabetic nephropathy.

2. Evidence Acquisition

Directory of Open Access Journals (DOAJ) Google Scholar, Pubmed (NLM), LISTA (EBSCO) and Web of Science were searched with key words relevant to ACE I/D polymorphism, ACE activity, Diabetic nephropathy, ACE inhibitors, Angiotensin II receptor blockers.

3. Results

55 research and review articles relevant to this topic directly or indirectly have been found. From the information given in these papers, the following aspects were drawn out.

Diabetic nephropathy (DN) is one of the major microvascular complications of diabetes and is the leading cause of end-stage renal disease (ESRD). In one-third of type 2 diabetes mellitus (T2DM) patients with excellent blood glucose control DN is developed, while in most patients even with suboptimal blood glucose control and antihypertensive therapy DN is not appeared. Therefore, a genetic susceptibility to diabetic nephropathy has been proposed (1-3).

3.1 Angiotensin converting enzyme (ACE) gene Polymorphism

Angiotensin converting enzyme (ACE) gene is one of the most studied gene to be involved in the pathogenesis of diabetic nephropathy including micro- and macro-albuminuria and progression from micro- to macro-albuminuria. The ACE gene is located on the long arm of chromosome 17 (17q23) and has 21 kilo bases long containing 26 exons and 25 introns. More than 160 ACE gene polymorphisms are known that most of them are single nucleotide polymorphisms. Rigat et al. (4), for the first time, reported the ACE insertion (I)/deletion (D) polymorphism of involving the presence (insertion) and absence (deletion) of a 287-bp sequence of DNA in intron 16 of the gene. This polymorphism is one of the most studied polymorphism in diabetic nephropathy.

The frequency of ACE alleles varies in different ethnic groups and might contribute to the conflicting results related to the role of ACE (I/D) polymorphism in diabetic nephropathy (5, 6).

This polymorphism is detected using a polymerase chain reaction (PCR) method reported by Rigat et al. (4). However, due to mistyping of around 4-5% ID genotype as DD genotype an additional and confirmatory PCR using a new sense insertion specific primer has been introduced (7).

3.2 ACE I/D polymorphism and plasma ACE activity

The physiological importance of ACE I/D polymorphism is its association with plasma ACE activity. The presence of DD genotype of this polymorphism is associated with 2-fold increased ACE activity, whereas those with the II genotype have the lowest ACE expression. This polymorphism is accounted for approximately half (47%) variation in ACE activity (8, 9).

In diabetic patients with nephropathy there is higher ACE activity compared with diabetic pa-

tients without nephropathy (10). Nikzamir et al. (11) demonstrated an association between ACE genotype and ACE activity with higher level of ACE in macroalbuminuric T2DM patients carrying the D allele in Tehran, a cosmopolitan city and capital of Iran. However, in the study of Fellehgari et al. (5) insignificant increase in the activity of ACE according to ACE genotype in diabetic patients with and without nephropathy from western Iran was detected. Their study indicated macroalbuminuric patients with ID and ID + DD genotypes had significantly higher ACE activity compared to those in normoalbuminuric patients with the same genotypes.

3.3 ACE I/D polymorphism: Onset and progression of diabetic nephropathy

In diabetic patients hyperglycaemia increases tissue angiotensin II which induces oxidative stress, glomerular hyperfilteration, endothelial damage, thrombosis, inflammation and vascular remodeling (12). DN is started with various renal functional changes including glomerular hyperfiltration and hyperperfusion, and increased glomerular filtration rates (GFR). DN is manifested with microalbuminuria that subsequently can progress to macroalbuminuria (13, 14). The ACE is a key component of renin angiotensin system (RAS) that plays an important role in blood pressure homeostasis by generating the vasoconstrictor peptide angiotensin II and by inactivating the vasodilator peptides bradykinin and angiotensin (1-7,15). ACE regulates microcirculation within the kidney through generating angiotensin II and in the presence of ACE D allele, the GFR increases in correlation with ACE plasma levels (1, 16).

The role of ACE I/D polymorphism in the pathogenesis of DN has been investigated in various ethnic groups with inconsistent results (6, 11, 17, 18). Ethnicity is one of the most important factors, which determines the role of ACE gene polymorphism in the susceptibility to DN. ACE D allele in Caucasians is not associated with DN. However, in Asian populations an association between ACE D allele and DN has been reported (10). In the French population the ACE I/D polymorphism was associated with DN. Also, in a larger European population including French, Danes and Finns this polymorphism was significantly associated with increased risk of DN (19). In T2DM patients from Tehran the presence of the D allele of ACE was associated with higher ACE activity and increasing severity of albuminurea (11, 20). Further, in Asian Indian and Tunisian patients with diabetic nephropathy the frequency of the D allele and the DD genotype was significantly increased compared with diabetic without nephropathy (21, 22). In a meta-analysis by Staessen et al. (23) it was reported that DD genotype of ACE I/D polymorphism versus II genotype is associated with 1.56-fold increased risk of diabetic nephropathy. In subsequent two separate meta-analyses by Ng et al. (18, 24) the protective role of II genotype against diabetic nephropathy especially among Asians (Chinese, Japanese, and Koreans) than Caucasians was confirmed. They indicated that the presence of ACE II genotype especially in Asian with T2DM was associated with lower risk for macroalbuminuria but was only marginally associated with the risk of microalbuminuria. In more recent meta-analysis (25), a 1.27-fold increased risk of diabetic nephropathy was detected for the presence of DD versus II genotype and was suggested as contribution of ACE I/D polymorphism in the development of DN especially among Asian T2DM patients. The protective effect of the ACE II genotype against nephropathy could be attributed to lower ACE activity and angiotensin

II bioavailability (19, 26). In the presence of both ID and DD genotypes the GFR increased in correlation with ACE plasma levels (27).

In contrast, among Caucasians French, Turkish and Tunisian populations the ACE I/D polymorphism was not a marker for DN and renal prognosis of patients with T2DM (6, 16, 17, 28). Also, among Iranians with Kurdish ethnic background ACE I/D polymorphism was not associated with the risk of microalbuminuria (10). It has been suggested that unlike macroalbuminuria, microalbuminuria does not necessarily reflect structural kidney damage and may be associated with insulin resistance, endothelial dysfunction, obesity, heart failure, and other clinical conditions that may not be affected by ACE I/D polymorphism or race (12). Moreover, among Mexican patients there were no differences in ACE I/D genotype distribution between patients with and without albuminuria (29).

In patients who develop macroalbuminuria, there is a progression from micro- to macro-albuminuria, reduction of renal function and hypertension (30). Due to the influence of genetic factors and metabolic control in the pathogenesis of DN, its development varies among diabetic patients (31). The role of ACE I/D polymorphism in the development of DN to ESRD in T2DM patients has been demonstrated by a recent meta-analysis (32). In contrast, Manea et al. (33) found a protective role for the D allele of ACE against diabetic nephropathy.

3.4 ACE I/D polymorphism and response to therapy

Transition from normoalbuminuria to macroalbuminuria increases the risk of renal and cardiovascular disease. To reduce the risk of ESRD, myocardial infarction and stroke the blood pressure and urinary albumin secretion should be decreased (14). ACE inhibitors with decreasing angiotensin II production decrease glomerular hypertension and glomerular permeability to urinary albumin resulting in reduced proteinuria. Angiotensin receptor blockers bind to angiotensin type 1 receptors (AT1R) and blocks it (14). Coexistence of hypertension and T2DM increase the risk of kidney damage. Angiotensin II receptor blockers and ACE inhibitors improve markers of kidney disease and slow kidney disease progression in diabetic and non-diabetic patients (34).

The presence of ACE I/D polymorphism in T2DM patients affects on the response to ACE inhibitor and angiotensin II receptor antagonists therapy. During about 3 years treatment of Japanese patients with a combination of ACE inhibitors and angiotensin receptor antagonists in carriers of II and ID genotypes proteinurea decreased (35). In contrast, in a large study among Italian patients during 10 years treatment a greater health benefit of ACE inhibitors in carriers of DD genotype compared with ID or II genotypes has been observed (36). It has been demonstrated that T2DM patients with normo- or micro-albuminuria carrying I allele had a better response to ACE inhibitor therapy compared to those patients with D allele. While, in T2DM with overt nephropathy and D allele there was a better response to angiotensin II receptor antagonists therapy compared to I allele (5, 12, 37, 38). Similar comparable results were obtained in T1DM (39). In T1DM with microalbuminuria treated with ACE inhibitor of lisinopril or placebo a significantly reduced albuminuria by 51.3% in carriers of II genotype compared to 7.7% in those patients with DD genotype has been reported (39). The protective effect of treatment with ACE inhibitors against development and progression of nephropathy might be through more effective reduction in glomerular capillary

hydraulic pressure in patients with the II than in those with the DD genotype (40). The enhanced progression of kidney function loss in patients with DD and ID genotypes is resulting from increased internal activity of ACE and angiotensin II receptor antagonists has the greatest beneficial effects on patients with DD and ID genotypes (41). However, Andersen et al. (42) suggested that in T1DM patients short term renoprotective (antiproteinuric) effect of angiotensin II receptor antagonist (losartan) is similar in both ACE II and DD genotypes. It has been suggested that ACE inhibitor therapy might be more benefit in the early stages of diabetic nephropathy, whereas in more advanced stages treatment appears to confer consistent renoprotection to all patients regardless of their ACE I/D genotypes (5). Among patients with overt nephropathy (43) an association between the I allele with a slower progression to doubling of serum creatinine or ESRD was observed. Also, it has been demonstrated that GFR decline over time was significantly slower in patients carrying one or two copies of I allele compared to D allele (44).

3.5 Interaction between ACE I/D and variants of RAS genes

The role of two genes variants of angiotensinogen (AGT) and angiotensin II type-1 receptor (AT1R) and their interaction with ACE I/D polymorphism on the susceptibility to DN has been investigated with controversy (47-50).

The common polymorphism of AGT T704C (M235T variant) gene encodes threonine instead of methionine at residue 235 in exon 2. The presence of 704C allele is associated with increased AGT levels (45). Also, A polymorphism in the promoter region of AGT at position -217 (G: A) affects baseline activity of the AGT promoter and is associated with hypertension (46).

Angiotensin II which results from enzymatic reaction of ACE on angiotensin I binds to angiotensin II type-1 receptor (AT1R). Interaction of (AT1R) A1166C polymorphism with ACE I/D polymorphism on the risk of development of DN has been investigated in few studies.

Lovati et al. (47) observed that there is a strong interaction between ACE DD and AGT TT genotype on the rapid progression of renal disease in ESRD patients. Jacobsen et al. (48) observed an interaction between ACE I/D, AGT M235T and AT1R A1166C on the progression of diabetic nephropathy in T1DM patients. They suggested a concomitant presence of various gene variants resulting in synergistic activation of RAS that is not compensate by system. Bantis et al. (49) reported an association between concomitant presence of ACE I/D and AGT M235T variants on the progression of IgG nephropathy to ESRD and better response to ACE inhibitor therapy in the presence of these variants. However, Subsequent report of Osawa et al. (50) failed to indicate any significant interaction between ACE I/D, AGT M235T and AT1R A1166C variants on the risk of DN.

3.6 Interaction of ACE I/D polymorphism with eNOS gene polymorphism

Nitric oxide synthase (NOS) synthesizes NO through the oxidation of L-arginine to L-citrulline, which is an important regulator of vasodilator tone and blood pressure (51).

A 27-bp long repeat in the fourth intron of endothelial NOS (eNOS) designated as the 4a/4b polymorphism has been reported that in the presence of ACE I/D or M235T polymorphism increased the risk of renal disease progression (52).

The G894T polymorphism in exon 7 of the eNOS gene is one of the most clinically impor-

tant polymorphisms of eNOS. The presence of this polymorphism causes reducing NO level and is associated with essential hypertension and has been implicated in the pathogenesis and development of DN (30, 51).

A trend toward increased risk of DN in T2DM patients in the presence of both ACE D and eNOS 894 T alleles has been reported (30). This effect could be attributed to the increasing activity of ACE and angiotensin II level in the presence of D allele and decreasing NO production in the presence of T allele, which accelerate diabetic nephropathy (30). However, lack of synergistic effects between two polymorphisms and the risk of DN has been reported (3).

3.7 Interaction of ACE I/D polymorphism with MTHFR variants

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme involved in the metabolism of homocysteine. The role of hyperhomocysteinemia in the pathogenesis of DN has been indicated (28). The transition of C to T at nucleotide 677 of the MTHFR gene causes an alanine to valine exchange at position 222 that produces a thermolabile enzyme with reduced catalytic activity (28, 53, 54). However, a different polymorphism in the MTHFR gene, the A1298C point mutation, may affect enzyme regulation (53-55).

The association between concomitant presence of ACE I/D polymorphism with either MTHFR C677T or A1298C polymorphism and increased risk of DN among patients with T2DM has been demonstrated and has suggested a strong interaction between MTHFR 1298 C allele and the ACE D allele with highly increased risk of DN (1). It seems the presence of variations in more genes instead of a single genetic defect play a role in the susceptibility to DN.

4. Conclusions

Most studies confirmed that, ACE I/D polymorphism is involved in the susceptibility to overt nephropathy with protective role of ACE II genotype against the disease in both T1DM and T2DM. Conflicting results from various studies related to the role of ACE I/D polymorphism in the development of DN could be attributed to the ethnic background of studied patients, gene–environment interaction, differences in the stage of nephropathy, sample size and the duration of diabetes. Also, the presence of ACE I/D polymorphism in T2DM patients affects the response to ACE inhibitor and angiotensin II receptor antagonists therapy with a better response to ACE inhibitor therapy in T2DM patients with normo- or micro-albuminuria carrying I allele. While, in T2DM with overt nephropathy and D allele there was a better response to angiotensin II receptor antagonists therapy compared to I allele. Synergistic effect of ACE I/D polymorphism with other gene variants of RAS or eNOS and MTHFR on the risk of DN might be ethnic dependent.

Conflict of interest

The author declared no competing interests.

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