Table 2. Summary of Included Studies Examining ACE I/D Polymorphism in Relation to Diabetic Nephropathy and Comorbidities

First author, year	Study design	Method of ACE I/D genotyping	Diabetic Nephropathy assessment	Results / conclusion	Studies Reported on ACE I/D polymorphism and mortality/ comorbidities in DN
Aggarwal et al., 2017	Cohort	Polymerase chain reaction RFLP	Albumin-creatinine ratio	ACE inhibitor therapy reduced ACR in 50% of DN patients, with response independent of ACE I/D and AGT M235T polymorphisms.	No
Araz et al., 2001	Cross-sectional	Polymerase chain reaction	Albumin-creatinine ratio	No link found between ACE I/D polymorphism and DN or DR in Turkish T2DM patients.	Yes
Arfa et al., 2008	Case-control	Polymerase chain reaction	Albumin Excretion rate	Preliminary findings show no association between ACE I/D polymorphism, T2DM, or DN in Tunisians.	No
Degirmenci et al., 2005	Cross-sectional	Polymerase chain reaction	Albumin-creatinine ratio	DD genotype linked to highest ACE activity; ID poses neuropathy risk, II protective; DD/ID may predict DR with longer diabetes duration.	Yes
Doi et al., 1996	Case-control	Polymerase chain reaction	Albumin-creatinine ratio	D allele linked to DN but not DR in Japanese NIDDM patients; no difference in	Yes

				genotype between controls and uncomplicated diabetics.	
Ergen et al., 2004	Case-control	Polymerase chain reaction	Albumin Excretion rate	No link between ACE polymorphism and DN, but DD genotype more frequent in T2DM vs. controls.	No
Ezzidi et al	Case-control	Polymerase chain reaction	Albumin-creatinine ratio	Specific ACE variants and DN-related haplotypes linked to DN pathogenesis in Tunisian T2DM patients.	No
Fathi et al., 2015	Case-control	Polymerase chain reaction and RFLP	Albumin Excretion rate	ACE-D and VEGF-G alleles identified as independent risk factors for microalbuminuria in T2DM patients.	No
Felehgari et al., 2011	Case-control	Polymerase chain reaction	Albumin-creatinine ratio	Findings highlight ethnic influence on DN development and genotype-specific therapy responses in Kurdish T2DM patients.	No
Grzeszczszak et al., 1998	Case-control	Polymerase chain reaction	Albumin-creatinine ratio	No association found between ACE I/D, PstI polymorphisms and nephropathy in NIDDM.	No
Gupta et al., 2023	Cross-sectional	Polymerase chain reaction	Albumin-creatinine ratio	VEGF D allele linked to DR in DN patients, highlighting VEGF's role in retinopathy.	Yes
Ha et al., 2000	Case-control	Polymerase chain reaction	Albumin-creatinine ratio	ACE gene polymorphisms might have a role in determining ACE inhibitor responsiveness	No

				among proteinuric NIDDM patients.	
Ha et al., 2003	Cohort	Polymerase chain reaction	Albumin-creatinine ratio	ACE DD genotype identified as a potential risk factor for DN progression in Korean T2DM patients.	No
Hadjadj et al., 2003	Cohort	Polymerase chain reaction	Albumin Excretion rate	No association found between ACE I/D polymorphism and albuminuria in French T2DM patients.	No
Hsieh et al., 2000	Cohort	Polymerase chain reaction	Albumin Excretion rate	ACE DD genotype is markedly high in T2DM and it is significantly associated with DN	No
Huang et al., 1998	Cohort	Polymerase chain reaction	Albumin Excretion rate	9-year follow-up found no evidence that ACE I/D polymorphism is a major genetic marker for DN in NIDDM patients.	No
Ismail et al., 2017	Case-control	Polymerase chain reaction	Albumin-creatinine ratio	ACE DD, TCF7L2 T allele, and PPARGC1A A allele linked to DN risk; these polymorphisms may serve as susceptibility markers in T2DM.	No
Jayapalan et al., 2010	Case-control	Polymerase chain reaction with sequencing	Albumin-creatinine ratio	ACE I/D polymorphism not linked to T2DM or DN in Malaysian population, irrespective of ethnicity or gender.	No

Kiconco et al., 2024	Cross-sectional	Polymerase chain reaction	Microalbuminuria	ACE I/D affects metabolic markers, not nephropathy; recommends guideline inclusion.	No
Kimura et al., 1998	Cohort	Polymerase chain reaction with sequencing	Albumin Excretion rate	ACE DD and PAI-1 4G4G genotypes are independent risk factors for macroangiopathy, not DN progression, in NIDDM; combined genotyping may aid in predicting vascular events.	No
Kuramoto et al., 1999	Cross-sectional	Polymerase chain reaction	Albumin Excretion rate	ACE D allele linked to increased DN risk in NIDDM patients with insulin resistance.	No
Lee YJ and Tsai JC 2002	Cross-sectional	Polymerase chain reaction	Albumin-creatinine ratio	ACE I/D polymorphism linked to metabolic syndrome in Chinese T2DM, implicating RAS in metabolic dysfunction.	Yes
Luo et al., 2019	Case-control	Polymerase chain reaction with sequencing	Albumin Excretion rate	ACE gene at the rs4646994 locus may increase the risk of developing T2DN	No
Mahwish et al., 2020	Case-control	Polymerase chain reaction	Albumin Excretion rate	ACE DD genotype linked to higher DN risk, while ID genotype showed protective effect in dyslipidemic T2DM patients.	No
Mansoor et al., 2010	Case-control	Polymerase chain reaction	Albumin Excretion rate	ACE I allele linked to DN progression in Pakistani men, not women; neuropathy and family history also key factors.	No

Mansouri et al., 2017	Case-control	Polymerase chain reaction	Albumin-creatinine ratio	D allele most common in Moroccans; ACE I/D polymorphism not linked to DN risk.	No
Movva et al., 2007	Case-control	Polymerase chain reaction	Albumin Excretion rate	D allele linked to increased DN risk in Asian Indians with T2DM.	No
Nikzamir et al., 2009	Cross-sectional	Polymerase chain reaction	Albumin Excretion rate	In Iranian T2DM patients, D allele is linked to albuminuria progression, not its onset.	No
Ohno et al.,1996	Cross-sectional	Polymerase chain reaction and RFLP	Albumin Excretion rate	ACE D allele linked to higher ACE activity and abnormal albuminuria; ACE I/D, not AGN M235T, is a DN risk factor in Japanese NIDDM.	No
Okuno et al., 2003	Cohort	Polymerase chain reaction	Albumin Excretion rate	ACE D allele identified as a strong independent risk factor for microalbuminuria in T2DM patients.	No
Oue et al., 1999	Cohort	Polymerase chain reaction	Albumin-creatinine ratio	ACE DD genotype, poor glycemic control, and older age identified as key risk factors for microalbuminuria progression in Japanese T2DM patients.	No
Parchwani et al., 2013	Case-control	Polymerase chain reaction	Albumin Excretion rate	ACE DD variant linked to higher DN risk, not severity, in T2DM.	No
Pawar et al., 2024	Cross-sectional	Polymerase chain reaction	Albumin-creatinine ratio	ACE DD and AGT Met235Thr genotypes significantly	No

				associated with increased risk of DN and DR in T2DM patients, highlighting RAAS gene variants as potential genetic markers.	
Rahimi et al., 2012	Case-control	polymerase chain reaction (PCR) and PCR-restriction fragment length polymorphism (PCR-RFLP)	Albumin-creatinine ratio	ACE D and eNOS T alleles individually showed no significant DN risk, but their combined presence was associated with a fivefold increased risk of macroalbuminuria, suggesting a synergistic effect.	No
Schmidt et al., 1995	Cross-sectional	Enhanced primers with DMSO	Albumin Excretion rate	No significant association found between ACE I/D polymorphism and nephropathy in either type 1 or type 2 diabetes, despite large sample size and long disease duration.	No
Shaihk et al., 2014	Cross-sectional / case-control study.	Polymerase chain reaction and ARMS	RFTs	ACE D allele and AGT T allele identified as genetic risk factors for diabetic nephropathy.	No
Solini et al., 1999	Observational	Polymerase chain reaction and RFLP	Albumin Excretion rate	No link found between ACE/AGN polymorphisms and albuminuria in T2DM families.	No
Tseng et al., 2010	Cross-sectional	Polymerase chain reaction	Albumin-creatinine ratio	ACE DD genotype, combined with hypertension, smoking, dyslipidemia, and obesity, significantly contributes to	No

				albuminuria in Taiwanese T2DM patients.	
Uddin et al., 2007	Case-control	Polymerase chain reaction	Albumin Excretion rate	Percentage of DD genotype and D allele was significantly higher in DN compared to controls.	No
Viswanathan et al., 2001	Case-control	Polymerase chain reaction	Albumin-creatinine ratio	D allele linked to nephropathy; no ID/DD distribution difference.	No
Wang et al., 2016	Cross-sectional	Polymerase chain reaction	Albumin-creatinine ratio	ACE I/D polymorphism linked to DKD onset in T2DM; DD genotype showed greatest renoprotective response to valsartan.	No
Wyawahare et al., 2017	Cross-sectional	Polymerase chain reaction	Albumin-creatinine ratio	ID genotype most common; no link to albuminuria levels.	No
Yahya et al., 2024	Cross-sectional	Polymerase chain reaction	Albumin-creatinine ratio	DD genotype linked to 2× DN risk; AGT1R A1166C not associated with DN in Iraqi T2DM	No
Yahya et al., 2024	Cross-sectional	HRM-RT and PCR-RFLP.	Albumin-creatinine ratio	ID and AC genotypes linked to lower ACE1/2, lower ACR, better ACEI response.	No
Yoshida et al., 1996	Cohort	Polymerase chain reaction	Albumin Excretion rate	ACE DD genotype strongly predicts progression to ESRD in NIDDM patients with albuminuria and is linked to higher mortality after dialysis initiation.	Yes

Young et al., 1998	Case-control	Polymerase chain reaction	Albumin Excretion rate	High AGT TT genotype and T allele frequencies may underlie elevated albuminuria rates in Chinese T2DM; potential synergism with ACE D allele warrants further study.	No

This table provides a summary of selected studies investigating the association between angiotensin-converting enzyme (ACE) I/D polymorphism and diabetic nephropathy (DN) among patients with type 2 diabetes mellitus (T2DM). It includes details on study design, methods of ACE I/D genotyping, approaches used to assess DN (albumin-to-creatinine ratio, albumin excretion rate, or microalbuminuria), main findings or conclusions, and whether mortality or comorbid conditions (such as retinopathy, cardiovascular disease) related to ACE I/D polymorphism were reported. Most studies employed polymerase chain reaction (PCR) techniques for genotyping and utilized albumin-based measures to assess nephropathy. While several studies reported a significant association between the D allele or DD genotype and DN, comorbidity and mortality data were less frequently examined or reported.

Abbreviations: ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; AGT, angiotensinogen; AGT1R, angiotensin II type 1 receptor; ALR2, aldose reductase 2; DD, homozygous deletion genotype; DN, diabetic nephropathy; DR, diabetic retinopathy; HRM-RT, high-resolution melt real-time; ID, heterozygous insertion/deletion genotype; I/D, insertion/deletion; NIDDM, non-insulin-dependent diabetes mellitus; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction–restriction fragment length polymorphism; T2DM, type 2 diabetes mellitus; VEGF, vascular endothelial growth factor.