Revista Eletrônica
Acervo Saúde
Electronic Journal Collection Health ISSN 2178-2091

Association of I/D polymorphism in the ACE gene and the susceptibility of patients to diabetic neuropathy

Associação do polimorfismo I/D no gene da ECA e a suscetibilidade de pacientes à neuropatia diabética

Asociación del polimorfismo I/D en el gen de la ECA y la susceptibilidad de los pacientes a la neuropatía diabética

Georgia Silva Menezes[1], Pedro Luiz de Paiva[1], Kamilla de Faria Santos[1], Angela Adamski da Silva Reis[2], Rodrigo da Silva Santos[2].

ABSTRACT

Objective: We conducted a systematic review and meta-analysis to evaluate the association between polymorphisms in the ACE and ACE2 genes and the development of diabetic neuropathy (DN). **Methods:** We searched six databases (NCBI/PubMed, MEDLINE, Cochrane Library, Virtual Health Library, Scielo, and Embase) as well as grey literature (Google Scholar and citations). Two independent reviewers selected the articles according to predefined inclusion and exclusion criteria. **Results:** The systematic literature search identified 114 records across the databases. At the end of the selection process, 5 studies were included in the qualitative analysis, and 4 studies were included in the quantitative analysis. All included studies were case-control studies conducted in Iraqi, Pakistani, and Turkish populations. **Conclusion:** According to the meta-analysis, the ID+DD genotypes of the ACE gene I/D polymorphism are associated with an increased risk of developing DN (OR = 1.43, CI = 1.01–2.03, p = 0.0464). Our analysis also suggests that the D allele is a risk marker for DN (OR = 1.42, CI = 1.19–1.68, p < 0.0001), with similar findings previously reported. Further observational studies in diverse populations are needed to confirm this association.

Keywords: Diabetic neuropathy, Angiotensin-converting enzyme, INDEL mutation, Meta-analysis.

RESUMO

Objetivo: Realizamos uma revisão sistemática e meta-análise para avaliar a associação entre polimorfismos nos genes ECA e ECA2 e o desenvolvimento de ND. **Métodos:** Buscamos registros em seis bases de dados (NCBI/PubMed, MEDLINE, Biblioteca Cochrane, Biblioteca Virtual em Saúde, Scielo e Embase) e na literatura cinzenta (Google Scholar e citações). Dois revisores independentes selecionaram os artigos de acordo com os critérios de inclusão e exclusão definidos. **Resultados:** A busca sistemática da literatura identificou 114

[1] Neurogenetics Research Center, Institute of Biological Sciences, Federal University of Goiás (UFG), Goiânia - GO.
[2] Department of Biochemistry and Molecular Biology, Institute of Biological Sciences, Federal University of Goiás - Goiânia, GO.

SUBMETIDO EM: 8/2025 | **ACEITO EM: 9/2025** | **PUBLICADO EM: 10/2025**

registros nas bases de dados. Ao final da seleção, 5 estudos foram incluídos na análise qualitativa e 4 estudos foram incluídos na análise quantitativa. Todos os estudos incluídos foram estudos de caso-controle e realizados nas populações iraquiana, paquistanesa e turca. **Conclusão:** De acordo com a metanálise, os genótipos ID+DD do polimorfismo I/D do gene da ECA estão associados a um risco aumentado de desenvolvimento de ND (OR=1,43, IC=1,01-2,03, p=0,0464). Nossa análise sugere ainda que o alelo D também é um marcador de risco para ND (OR = 1,42, IC = 1,19–1,68, p < 0,0001), e resultados semelhantes foram encontrados anteriormente. Mais estudos observacionais em diferentes populações são necessários para confirmar esta associação.

Palavras-chave: Neuropatia diabética, Enzima conversora de angiotensina, Mutação INDEL, Metanálise.

RESUMEN

Objetivo: Realizamos una revisión sistemática y un metaanálisis para evaluar la asociación entre los polimorfismos en los genes ECA y ECA2 y el desarrollo de la neuropatía diabética (ND). **Métodos:** Se realizaron búsquedas en seis bases de datos (NCBI/PubMed, MEDLINE, Biblioteca Cochrane, Biblioteca Virtual en Salud, Scielo y Embase), así como en literatura gris (Google Scholar y citas). Dos revisores independientes seleccionaron los artículos de acuerdo con los criterios de inclusión y exclusión previamente definidos. **Resultados:** La búsqueda sistemática de la literatura identificó 114 registros en las bases de datos. Al finalizar la selección, se incluyeron 5 estudios en el análisis cualitativo y 4 estudios en el análisis cuantitativo. Todos los estudios incluidos fueron estudios de casos y controles realizados en poblaciones iraquí, paquistaní y turca. **Conclusión:** Según el metaanálisis, los genotipos ID+DD del polimorfismo I/D del gen ECA están asociados con un mayor riesgo de desarrollo de ND (OR = 1,43; IC = 1,01–2,03; p = 0,0464). Nuestro análisis también sugiere que el alelo D es un marcador de riesgo para ND (OR = 1,42; IC = 1,19–1,68; p < 0,0001), y resultados similares ya han sido reportados anteriormente. Se necesitan más estudios observacionales en diferentes poblaciones para confirmar esta asociación.

Palabras clave: Neuropatía diabética, Enzima convertidora de angiotensina, Mutación INDEL, Meta análisis.

INTRODUCTION

Among the main microvascular complications of Diabetes Mellitus (DM) are diabetic nephropathy, diabetic retinopathy and diabetic neuropathy (DN) (PARK S, et al., 2019). DN presents dependent sensorimotor impairment and can be divided into peripheral autonomic neuropathy and painful neuropathy (KHALAFKM, et al., 2019; PAPANAS N e ZIEGLER D, 2013).

The prevalence of DN in patients with type 2 DM (T2DM) is around 60%, and approximately a quarter is characterized as painful diabetic peripheral neuropathy (SPALLONE V e GRECO C, 2013). The pathophysiology of vascular complications resulting from DM is mainly associated with hyperglycemia, dyslipidemia, epigenetic and genetic regulation (PARK, et al., 2019).

Advanced glycation end products (AGEs) are molecules intimately involved in the pathogenesis of DN, leading to damage in neurons, mainly in sensory axons and subsequently in motor axons (KAKU M, et al., 2015; SEYEDIZADEH SH, et al., 2020). Sensory neurons, specifically within the dorsal root ganglion and peripheral sensory receptors, are susceptible to circulating toxic agents and high levels of glucose. After nerve damage, growth factors and inflammation mechanisms sensitize peripheral nociceptors, which contributes to the symptomatology of DN (BAKA P, et al., 2021; KOBAYASHI M e ZOCHODNE DW, 2018; KRAMES ES, 2014).

Additionally, the renin-angiotensin system (RAS) plays an important role in regulating electrolyte balance and metabolic processes, in this pathway we have key enzymes, such as Angiotensin-converting enzyme (ACE) and its homologue ACE2. ACE is an enzyme that converts angiotensin I (Ang I) into angiotensin II (Ang II). After the stimulus that occurs with the drop in blood pressure, prorenin cleavage reactions release the enzyme renin, which acts on the plasma protein angiotensinogen to release Ang I. Subsequently, two amino

acids are removed from Ang I, forming the peptide of eight amino acids Ang II, an extremely potent vasoconstrictor (GUYTON AC, et al., 2021).

The ACE gene has 26 exons and is located at 17q23.3 (TIKHOMIROVA VE, et al., 2017). The most studied polymorphism of this gene is characterized by the presence (insertion) or absence (deletion) of 287 bp in intron 16. This polymorphism (I/D) was associated with serum ACE concentrations, the D allele is related to the greater production of ACE when compared to the I allele (MONTGOMERYHE, et al., 1997; RIGATB, et al., 1990). The literature found an association between the ACE I/D genetic polymorphism and diabetic nephropathy, especially the D allele or the DD genotype in patients with T2DM and this microvascular complication (YU ZY, et al., 2012).

ACE2 has the opposite effect of ACE, it acts by producing Ang 1-7, which has the opposite action to Ang-II. The ACE2 gene is located on Xp22.2 and has been evaluated in susceptibility to several diseases, mainly due to its significant impact on the regulation of the RAS (DONOGHUE M, et al., 2000).

Regarding DN, a potential association between the ACE gene polymorphism and DN has been described (WU S, et al., 2017). However, a more assertive definition is needed about the relationship between the ACE and ACE2 genes and DN. Therefore, the aim of our study is to investigate whether polymorphisms in the ACE and ACE2 genes are associated with DN susceptibility.

METHODS

Search strategy

We conducted an extensive search of the following databases: National Center for Biotechnology Information (NCBI/ PubMed®), Medical Literature Analysis and retrieval system Oline (MEDLINE), Cochrane Library, Virtual Health Library (VHL), Scientific Electronic Library Online (SciELO), Embase and Google Scholar. We also use truncation symbols, such as the asterisk (*) in PubMed and Cochrane, and the dollar sign ($) in other databases, to enhance the search.

To select search terms, we used the PECOS strategy (P: population, E: exposure, C: comparison, O: outcomes, S: study type). The survey was registered as a review protocol (ID: CRD42021297326) on the international platform Prospective Register of Systematic Reviews (PROSPERO).

We were guided by the Preferred guide reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) (PAGE MJ, et al., 2021).

The terms pre-selected for the search strategy were: “polymorphism, genetic”; “DNA sequence analysis”; “human genetics”; “genes”; “diabetes mellitus”; “type 2 diabetes mellitus”; “type 1 diabetes mellitus”; “genetic polymorphism”, “type 2 diabetes mellitus”, “genetics”; "polymorphism"; “angiotensin I converting enzyme”; “angiotensin-converting enzyme 2” and “genetic association studies”. To complete the search strategy, we employ the boolean operators “AND” and “OR” to combine search terms.

Inclusion and exclusion of studies

We researched for studies that explored ACE polymorphisms as a risk factor for the development and progression of DN. For the systematic review, we applied the following inclusion criteria: 1) Studies in humans; 2) Adults and ethnicities from any country; 3) Individuals diagnosed with type 1 and/or type 2 DM; 4) Confirmed diagnosis of DN; 5) Studies evaluating ACE polymorphism and its correlation with DN; 6) Detection of ACE polymorphism using molecular biology techniques.

Exclusion criteria were: 1) Duplicate references; 2) Revisions and duplication of previous publications; 3) Methodologically inadequate studies and/or with insufficient methodological information; 4) Patients with neuropathy not related to DM or with no defined cause; 5) DM patients without type identification. Two independent reviewers selected the most suitable studies according to these criteria. In case of disagreement, both reviewers reached a consensus.

Selection of studies and assessment of methodological quality

Two independent reviewers (GSM and PLP) selected the studies for the two-phase systematic review. Rayyan software (OUZZANI M, et al., 2016) was used for selection. In the first phase, after excluding duplicates, both reviewers read the title and abstract of the studies found through the search strategy, selecting the articles that best suited the inclusion criteria. At the end of the first phase, the reviewers discussed all conflicting decisions and reached a consensus.

In the second phase, reviewers read the full article and applied the same inclusion and exclusion criteria. While reading the full document, both reviewers completed a critical appraisal form standardized by the Joanna Briggs Institute specific to each study design (INSTITUTE TJB, 2022). Only studies with a score of 7.0 or higher were included. Again, the reviewers discussed all conflicting decisions to reach a consensus.

Data extraction

We extract and summarize all data related to methods and results from the articles included in the systematic review. The following data were prospectively extracted: author and year of publication, country of publication, study design, abstract, main conclusions, age, sex, sample size (control and cases), mean duration of DM in years, genotypic and allelic frequencies.

Statistical analysis

All statistical tests were conducted using RStudio software (version 4.1.0). Test results were described graphically and numerically after compiling findings from included studies. We used the Higgins inconsistency test (I^2) to estimate the proportion of total variability in point estimates attributed to heterogeneity other than chance.

The meta-analytical model of choice considered the test of heterogeneity between studies, applying the fixed effect model (Mantel-Haenszel method) when I^2<25% (low heterogeneity), the random effects model (DerSimonian–Laird Method) when I^2 25–75% (moderate heterogeneity), and values >75% were defined as high heterogeneity.

Finally, Egger's regression asymmetry test (EGGER M, et al., 1997) was performed, visually presenting through the funnel plot to detect publication bias. A p-value <0.05 suggests a high probability of publication bias.

RESULTS

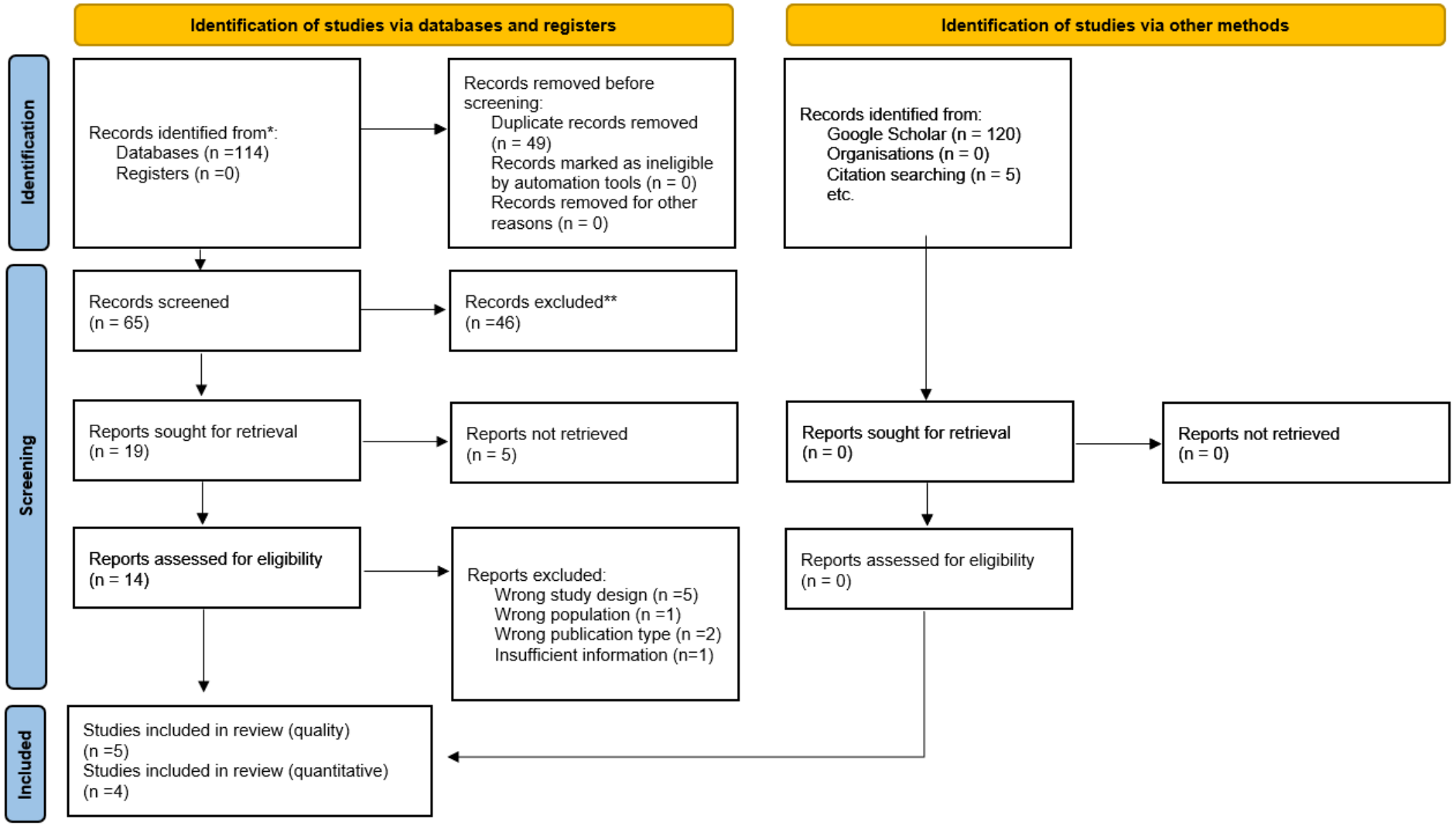
The systematic search in the literature identified 114 records in the databases. We exported the title and abstract of these records to Rayyan software (OUZZANI M, et al., 2016), where it was possible to identify and remove 49 duplicate studies.

After removing duplicate studies, we evaluated 65 titles and abstracts, of which 46 were excluded because they did not meet one or more inclusion criteria. The 19 studies that met the inclusion criteria were retrieved in full, free of charge on the web or by direct contact with the authors, five studies did not obtain response and were excluded.

The full texts of the 14 included studies were evaluated in detail regarding inclusion and exclusion criteria and submitted to a critical peer review process. After analysis, 5 (DEGIRMENCII, et al., 2005; DHUMAD MM, et al., 2020; INANIR A, et al., 2013; KHAN A, et al., 2021; SETTIN A, et al., 2015) studies were included in the qualitative analysis and 4 (DEGIRMENCI I, et al., 2005; DHUMAD MM, et al., 2020; INANIR A, et al., 2013; KHAN A, et al., 2021) studies were included in the quantitative analysis. The results of the literature search are presented in (**Figure 1**).

Regarding the assessment of methodological quality, for case-control studies, 9 parameters were applied, and the studies were homogeneous, individually reaching a minimum of 70% positive responses, being classified as having low risk of bias.

Figure 1 - PRISMA flowchart describing the steps for selecting articles for systematic review and meta-analysis.



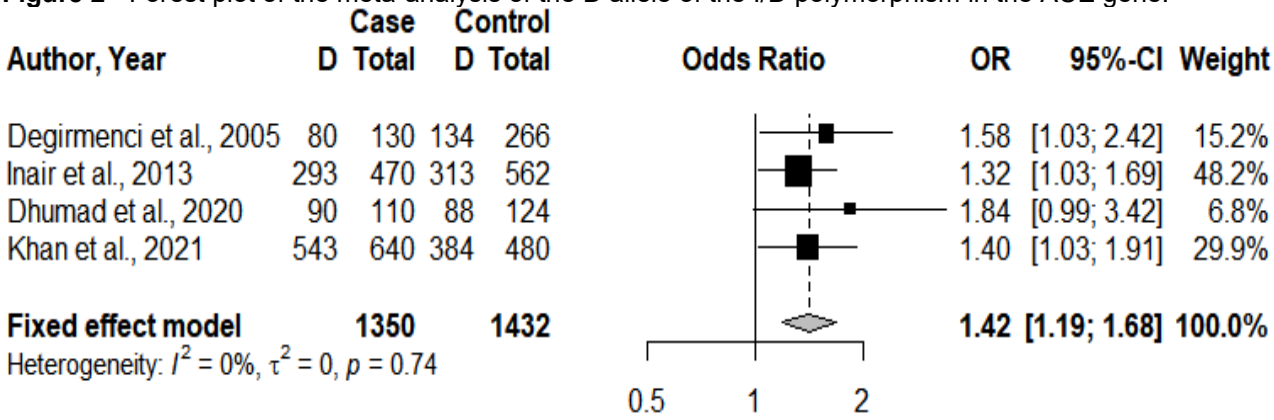
Source: Menezes GS, et al., 2025. Adapted from: Page MJ, et al., 2021.

All included studies were case-control studies and evaluated the I/D polymorphism of the ACE gene. No study was found associating polymorphisms in the ACE2 gene with DN. The control group consisted of 754 individuals and the case group included 762 individuals. In the study with 142 cases in the Iraqi population, the difference between genotypes II, DD and I/D was not considered significant (p= 0.054) for DN (DHUMAD MM, et al., 2020).

In the Pakistani population sample (cases = 320) the homozygous DD genotype of the ACE gene was found with significantly higher frequency in patients with DN (OR=1, 5818, p =0.012) (KHAN, et al., 2021). In Turkey, the DD genotype of the I/D polymorphism was a susceptibility factor for DN in the homozygous form (p = 0.032) (INANIR A, et al., 2013) and the ID genotype was suggested as a risk factor for DN, in addition to being associated with increased activity of ACE (DEGIRMENCI I, et al., 2005).

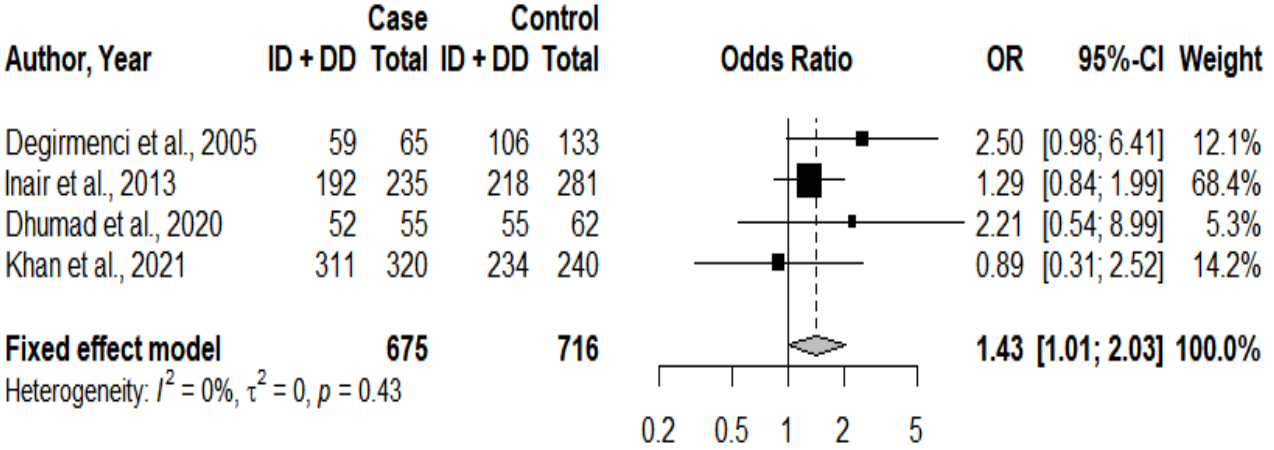
The meta-analysis using odds ratio showed that the D allele is positively associated with increased risk for DN (OR=1.42, CI=1.19–1.68, p<0.0001), with no evidence of significant heterogeneity (**Figure 2**). Furthermore, ID+DD genotypes also showed a correlation with increased risk for DN (OR=1.43, CI=1.01-2.03, p=0.0464), without evidence of significant heterogeneity (**Figure 3**).

Figure 2 - Forest plot of the meta-analysis of the D allele of the I/D polymorphism in the ACE gene.



Source: Menezes GS, et al., 2025.

Figure 3 - Forest plot of the meta-analysis of the ID+DD genotype of the I/D polymorphism in the ACE gene.

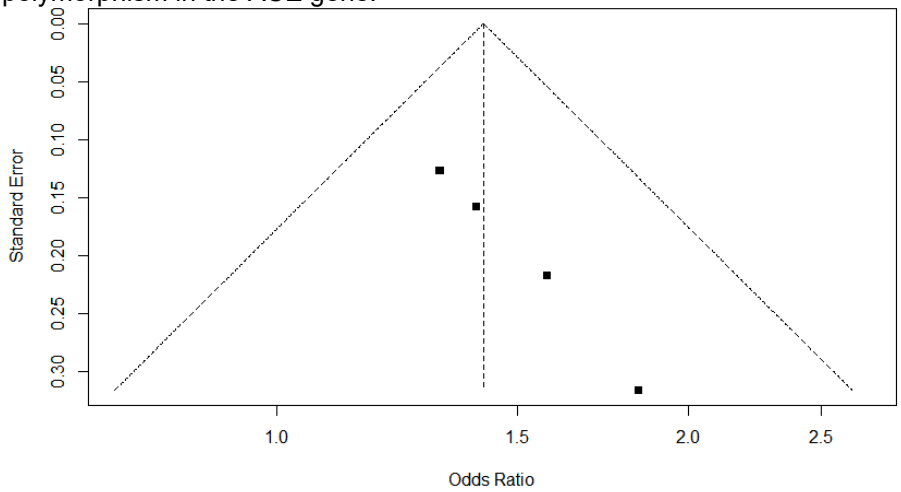


Source: Menezes GS, et al., 2025.

The publication bias analysis found no evidence of bias in line with the asymmetry observed in the funnel plots (**Figure 4** and **Figure 5**). Additionally, the Egger's test also did not show strong statistical evidence for publication bias (genotype, p=0.6057; allele, p=0.0020).

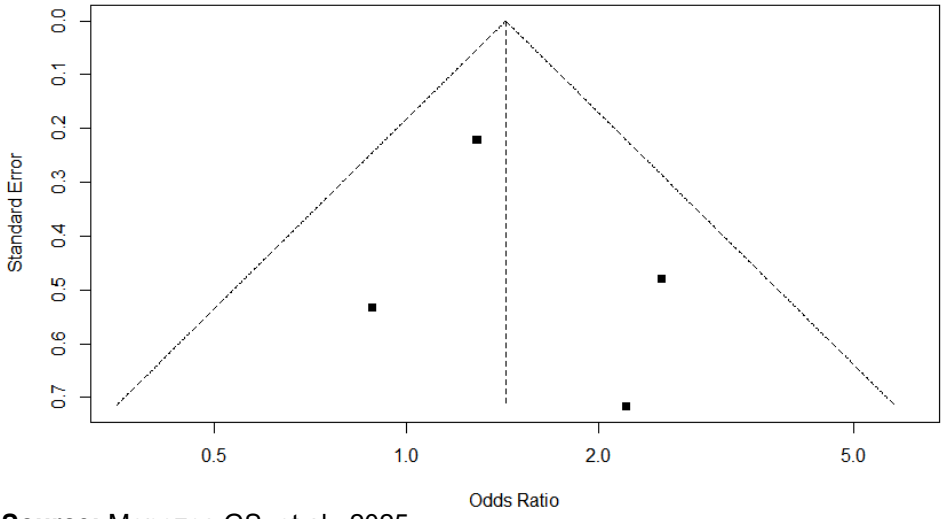
However, this analysis must be done with caution, as there is no guarantee of the reliability of these tests with fewer than 10 studies.

Figure 4 - Funnel plot of the meta-analysis of the D allele of the I/D polymorphism in the ACE gene.



Source: Menezes GS, et al., 2025.

Figure 5 - Funnel plot of the meta-analysis of the ID+DD genotype of the I/D polymorphism in the ACE gene.



Source: Menezes GS, et al., 2025.

DISCUSSION

ACE gene polymorphism is widely studied, its implications on outcomes involving macrovascular complications such as cardiovascular disease and, more recently, severe complications caused by SARS-CoV-2 dictate their relevance for precision health (COELHO DB, et al., 2022; GOREN T, et al., 2022; LUO R, et al., 2013). The relationship of the ACE gene with DM and its microvascular complications is also well established in the literature, however it still lacks more robust definitions in relation to DN (ITO H, et al., 2002; MARRE M, et al., 1994).

Our meta-analysis systematically investigated the association of ACE and ACE2 polymorphisms with DN susceptibility. Our results indicate that ID+DD genotypes of the ACE polymorphism are significantly associated with the risk of DN (Figure 3). Our data substantiate previous findings that addressed the influence of the ACE polymorphism on DN (LI Y E TONG N, 2015; RIGAT B, et al., 1990; WU S, et al., 2017).

The mechanisms involving the relationship between ACE and DN are broad, but it is known that ACE plays an important role in macro and microcirculation. The D allele of the ACE polymorphism has already been considered as a risk factor for DN in women with T2DM. The ACE I/D polymorphism is associated with changes

in enzyme levels in plasma, tissues and intracellular compartment. Previous trials observed that the DD genotype is related to a two-fold increase in the concentration of ACE activity compared to genotype II, this difference may be associated with greater susceptibility to microvascular complications in DM (COSTA AM, et al., 2009; DIAS RG, et al., 2007; MONTGOMERY HE, et al., 1997; STEPHENS JW, et al., 2005). On the other hand, genotype II seems to have a protective role for the development of DN in diabetic patients (MANSOOR Q, et al., 2012).

Genetic polymorphisms influence the pathogenesis of DN, as they may be involved in changes in microcirculation and metabolism of peripheral nerves. In this context, ACE is directly related to the biochemical-physiological axis of the renin-angiotensin system, which regulates blood pressure, fluid homeostasis and electrolyte balance, with repercussions on vasoconstriction, inflammation, oxidative stress and endothelial dysfunction, factors that contribute to peripheral nerve damage in DM (BAKA P, et al., 2021; COPPEY LJ, et al., 2006; FELDMAN EL, et al., 2019).

The development and progression of DN, associated with oxidative stress and vascular dysfunction, are described in the literature as having a positive relationship with ACE and its product (Ang II), which is deeply involved in the pathophysiology of endothelial damage and microcirculatory dysfunction, with reduced blood perfusion to peripheral nerves (BAKA P, et al., 2021; COPPEY LJ, et al., 2006; FELDMAN EL, et al., 2019).

The literature states that there is a strong relationship between the D allele and higher circulating levels of Ang II. Thus, the pathophysiological mechanism of DN is related to nervous damage that occurs from the microcirculation of the peripheral nerve, demonstrating that changes in the renin-angiotensin system can cause damage to peripheral nerves and consequences on susceptibility to DN and drastic complications, such as amputation (MOHAMMEDI K, et al., 2022; OLIVARES-REYES JA, et al., 2009). Our results also indicate an association of the D allele of the I/D polymorphism in the ACE gene with the risk of DN (Figure 2).

The studies included in this review are case-control studies, suitable for investigating diseases with a low incidence rate and diseases with a long latency period, in the latter group is DM (BELBASIS e BELLOU, 2018). Population genetics evaluates the control of diseases in groups of individuals related to the hereditary causes of diseases in populations, considering this scenario the ACE I/D polymorphism is a genetic biomarker associated with DM and DN in this population group. The present sample evaluated the Turkish, Iraqi and Pakistani populations, delimiting the sample to the Middle East population (DEGIRMENCI I, et al., 2005; DHUMAD MM, et al., 2020; HARTL, 2008; INANIR A, et al., 2013; KHAN A, et al., 2021).

In the study by Khan A, et al. (2021), in the Pakistani population, when evaluating the I/D polymorphism, the DD genotype had a higher prevalence among individuals with DN, as well as the D allele. In the study by Inanir A, et al. (2013), in Turkey, the DD genotype and the D allele were found as risk factors for DN, while in the study by Degirmenci I, et al. (2005), also carried out in Turkey, the ID genotype was more frequent in individuals with DN. On the other hand, Dhumad MM, et al. (2020), in the Iraqi population, did not observe a significant difference between the D and I alleles in the sample evaluated in their study.

In studies that evaluated populations in the Middle East, such as the one by El Alami H, et al. (2022) a significantly increased risk of susceptibility to T2DM was found in the Middle Eastern population with ACE gene polymorphism.

Musambil and Siddiqui (2019) confirmed the association of ACE polymorphism with the development of DM in the Arab population, while Mairghani M, et al. (2017) suggested a higher incidence and prevalence of diabetic foot ulcerations in Arab countries. Therefore, it can be inferred that this population group is more susceptible to DN, restricting the extrapolation of our findings to other populations.

Based on our results, it is understood that the D allele of the ACE gene polymorphism, as well as the ID+DD genotype, is associated with a higher risk for DN. The D allele is associated in the literature with higher circulating levels of Ang II (GUYTONAC, et al., 2021; OLIVARES-REYES JA, et al., 2009), additionally the pathophysiological mechanism of DN is related to the nervous damage that occurs from dysfunctions in the microcirculation of the peripheral nerve (GAO Y, et al., 2013; YOREK MA, 2015; ZHONG W, et al., 2017).

Therefore, our findings are relevant for understanding the mechanisms involved in microvascular complications in DM and subsequently targeting more effective treatments in precision health. However, it is important to emphasize that the study of ACE gene polymorphisms is only part of the complex nature of DN, considering that DM is a polygenic and multifactorial disease, other genetic and environmental factors also play an important role in susceptibility to the disease, and more research is needed to fully understand this relationship and its clinical implications.

Some limitations should be noted in our meta-analysis. First, we had a restricted number of studies included. However, this is justified by the scarcity of observational studies about DN and the ACE polymorphism. Secondly, the selected studies were from a geographically limited region. Although important ethnic differences occur between them, we cannot infer that the studies cover different geographic areas and ethnicities, such factors may influence the pooled results.

CONCLUSION

In conclusion, our meta-analysis confirms that the ACE I/D polymorphism is associated with an increased risk of developing DN. Our findings indicate that the ID+DD genotypes are the most strongly involved in the disease pathogenesis, supporting the consideration of the D allele as a risk marker for DN. Nevertheless, further observational studies are needed to investigate this association in diverse populations and to clarify the underlying mechanisms.

AUTHOR CONTRIBUTIONS

All authors were equally committed to conceiving the original idea, analyzing the data, interpreting the results and writing the article. All authors reviewed and approved the final version.

REFERENCES

1. BAKA P, et al. Systemic inflammatory biomarkers in painful diabetic neuropathy. J Diabetes Complications, 2021; 35(10): 108017.
2. BELBASIS L e BELLOU V. Introduction to Epidemiological Studies. Methods Mol Biol, 2018; 1793.
3. COELHO DB, et al. Polymorphism of the angiotensin converting enzyme gene (ACE-I/D) differentiates the aerobic and speed performance of football players. J Sports Med Phys Fitness, 2022: 62(2).
4. COPPEY LJ, et al. ACE Inhibitor or Angiotensin II Receptor Antagonist Attenuates Diabetic Neuropathy in Streptozotocin-Induced Diabetic Rats. Diabetes, 2006; 55(2).
5. COSTA AM, et al. Efeitos do sistema renina-angiotensina-aldosterona e do polimorfismo I/D do gene da ECA no desempenho esportivo. Rev Bras Ciências do Esporte, 2009; 31(1).
6. DEGIRMENCI I, et al. Frequency of angiotensin-converting enzyme gene polymorphism in Turkish type 2 diabetic patients. Int J Clin Pract, 2005, 59(10).
7. DHUMAD MM, et al. Angiotensin-converting enzyme insertion/deletion (I/D) gene polymorphism in Iraqi type 2 diabetic patients: association with the risk of cardiac autonomic neuropathy. Egyptian J Med Hum Genet, 2020; 21(1).
8. DIAS RG, et al. Polimorfismos genéticos determinantes da performance física em atletas de elite. Rev Bras Medicina do Esporte, 2007; 13(3).
9. DONOGHUE M, et al. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1–9. Circ Res, 2000; 87(5).
10. EGGER M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ, 1997; 315(7109).
11. EL ALAMI H,et al. Relationship between insertion/deletion (I/D) polymorphism of angiotensin converting enzyme (ACE) gene and susceptibility to type 2 diabetes mellitus in the Middle East and North Africa Region: A meta-analysis. Diabetes Metab Syndr, 2022; 16(1).
12. FELDMAN EL, et al. Diabetic neuropathy. Nat Rev Dis Primers, 2019; 5(1).

13. GAO Y, et al. Changes in nerve microcirculation following peripheral nerve compression. Neural Regen Res, 2013; 8(11).
14. GOREN T, et al. Investigation of Serum Angiotensin-Converting Enzyme (ACE) Concentration and ACE Gene Polymorphism in Patients With SARS-CoV-2 Pneumonia Admitted to the Emergency Department. Cureus, 2022; 14(11).
15. GUYTON AC, et al. Tratado de fisiologia médica. Rio de Janeiro: Grupo GEN, 2021; 14.
16. HARTL DL. Princípios de genética de população. FUNPEC, editor, 2008; 3.
17. INANIR A, et al. The importance of association between angiotensin-converting enzyme (ACE) Gene I/D polymorphism and diabetic peripheral neuropathy. Gene, 2013; 530(2).
18. INSTITUTE TJB. JBI Reviewer's Manual. Joanna Briggs Institute, 2022.
19. ITO H, et al. Angiotensin-converting Enzyme Insertion/Deletion Polymorphism and Polyneuropathy in Type 2 Diabetes without Macroalbuminuria. J Int Med Res, 2002; (30).
20. KAKU M, et al. Pathways in the Diagnosis and Management of Diabetic Polyneuropathy. Curr Diab Rep, 2015; 15(6).
21. KHALAF KM, et al. Vitamin B12 status and peripheral neuropathy in patients with type 2 diabetes mellitus. J Pak Med Assoc, 2019; 69(3).
22. KHAN A, et al. Association of ACE Gene Insertion/Deletion Polymorphism with Diabetic Peripheral Neuropathy in Population of Khyber Pakhtunkhwa Pakistan. Fresenius Environme Bulletin, 2021; 30(4).
23. KOBAYASHI M e ZOCHODNE DW. Diabetic neuropathy and the sensory neuron: New aspects of pathogenesis and their treatment implications. J Diabetes Investig, 2018; 9(6).
24. KRAMES ES. The Role of the Dorsal Root Ganglion in the Development of Neuropathic Pain. Pain Medicine, 2014; 15(10).
25. LI Y e TONG N. Angiotensin-converting enzyme I/D polymorphism and diabetic peripheral neuropathy in type 2 diabetes mellitus: A meta-analysis. J Renin Angiotensin Aldosterone Syst, 2015; 16(4).
26. LUO R, et al. The Influence of Angiotensin Converting Enzyme and Angiotensinogen Gene Polymorphisms on Hypertrophic Cardiomyopathy. PLoS One, 2013; 8(10).
27. MAIRGHANI M, et al. The prevalence and incidence of diabetic foot ulcers among five countries in the Arab world: a systematic review. J Wound Care, 2017; 26(9).
28. MANSOOR Q, et al. Angiotensin-converting enzyme (ACE) gene II genotype protects against the development of diabetic peripheral neuropathy in type 2 Diabetes Mellitus. J Diabetes, 2012; 4(3).
29. MARRE M, et al. Relationships Between Angiotensin I Converting Enzyme Gene Polymorphism, Plasma Levels, and Diabetic Retinal and Renal Complications. Diabetes, 1994; 43(3).
30. MOHAMMEDI K, et al. Association Between the ACE Insertion/Deletion Polymorphism and Risk of Lower-Limb Amputation in Patients with Long-Standing Type 1 Diabetes. Diabetes Care, 2022; 45(2).
31. MONTGOMERY HE, et al. Association of Angiotensin-Converting Enzyme Gene I/D Polymorphism with Change in Left Ventricular Mass in Response to Physical Training. Circulation, 1997; 96(3).
32. MUSAMBIL M e SIDDIQUI K. Genetics and genomics studies in type 2 diabetes: A brief review of the current scenario in the Arab region. Diabetes Metab Syndr, 2019; 13(2).
33. OLIVARES-REYES JA, et al.. Angiotensin II and the development of insulin resistance: Implications for diabetes. Mol Cell Endocrinol, 2009; 302(2).
34. OUZZANI M, et al. Rayyan - a web and mobile app for systematic reviews. Syst. Rev, 2016; 5(210).
35. PAGE MJ, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ, 2021; 372(71).
36. PAPANAS N e ZIEGLER D. Polyneuropathy in Impaired Glucose Tolerance: Is Postprandial Hyperglycemia the Main Culprit? A Mini-Review. Gerontology, 2013; 59(3).
37. PARK S, et al. Recent advances in the pathogenesis of microvascular complications in diabetes. Arch Pharm Res, 2019; 42(3).
38. RIGAT B, et al. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J Clinic Invest, 1990; 86(4).
39. SETTIN A, et al. Association of ACE and MTHFR genetic polymorphisms with type 2 diabetes mellitus: Susceptibility and complications. J Renin Angiotensin Aldosterone Syst, 2015; 16(4).

40. SEYEDIZADEH SH, et al. The Effects of Combined Exercise Training (Resistance-Aerobic) on Serum Kinesin and Physical Function in Type 2 Diabetes Patients with Diabetic Peripheral Neuropathy (Randomized Controlled Trials). J Diabetes Res, 2020.
41. SPALLONE V e GRECO C. Painful and Painless Diabetic Neuropathy: One Disease or Two? Curr Diab Rep, 2013; 13(4).
42. STEPHENS JW, et al. The D allele of the ACE I/D common gene variant is associated with Type 2 diabetes mellitus in Caucasian subjects. Mol Genet Metab, 2005; 84(1).
43. TIKHOMIROVA VE, et al. ACE phenotyping in human heart. PLoS One, 2017; 12(8).
44. WU S, et al. Effects of Common Polymorphisms in the MTHFR and ACE Genes on Diabetic Peripheral Neuropathy Progression: a Meta-Analysis. Mol Neurobiol, 2017; 54(4).
45. YOREK MA. Vascular Impairment of Epineurial Arterioles of the Sciatic Nerve: Implications for Diabetic Peripheral Neuropathy. Rev Diabet Stud, 2015; 12(1–2).
46. YU ZY, et al. Meta-analysis of the relationship between ACE I/D gene polymorphism and end-stage renal disease in patients with diabetic nephropathy. Nephrology, 2012; 17(5).
47. ZHONG W, et al. Improved neural microcirculation and regeneration after peripheral nerve decompression in DPN rats. Neurol Res, 2017; 39(4).