

Letter to the Editor

The Association between Apolipoprotein E Polymorphism and Diabetic Nephropathy in Iranian Patients

To the Editor,

We read with great interest the recently published article by Karimoei et al evaluating the association between apolipoprotein E (ApoE) polymorphism and diabetic nephropathy (DN) in a selected population of Iranian patients with diabetes mellitus (DM).¹ DN is the main cause of end-stage renal disease which affects approximately 35% of patients with DM.² While several predisposing risk factors including hyperglycemia, duration of DM, smoking, hypertension, age,^{3,4} and a positive family history have been identified,⁵ much of the mechanism by which DN develops in patients with DM remains unknown.⁶ As research in this area continues, much focus has been devoted to the genetic basis in recent years.⁷ ApoE is a plasma protein which contributes in lipid metabolism. ApoE gene is located on chromosome 19q and has 3 major alleles (2, 3, and 4) which are located on exon 4 of this gene.^{7,8} Several studies have investigated the association between ApoE polymorphism and development of DN; however, their findings were conflicting.⁷ There have been multiple studies showing association between 2 allele and development of DN,⁸⁻¹⁵ whereas, other studies have shown no correlation.¹⁶⁻¹⁹ Even more controversy surrounded 4 allele, as some studies have indicated 4 allele as a protective factor;^{8,14,20,21} while other studies have suggested this allele to be a risk factor of DN.^{17,19,22} Karimoei et al

in their study have shown protective effects of 4 allele on DN and found no association between 2 allele and DN in Iranian patients.¹ However, we believe that before making such a conclusion an important methodological issue should be considered.

In the index study, the age and duration of DM were significantly higher in patients with DN than patients without DN (61.5 ± 8.5 vs. 57.3 ± 8.1 , $P < 0.05$ and 12.01 ± 7.6 vs. 10.2 ± 6.9 , $P < 0.05$, respectively).¹ It is well-established that both age and duration of DM are two risk factors of DN.^{3,4} In fact when two study groups were not matched for these two factors the final conclusion may be misleading. Because by passing the time, probably, a number of patients with DM may eventually develop DN and this issue can make bias on allele frequency between the two groups. In other words, it is possible that some patients initially categorized as DM group without DN will eventually transfer to DN group over the ensuing years; hence, both age and DM duration adjustment are required to minimize the "bias of group transformation."

In other similar studies in the literature, this issue has been appreciated and the two study groups are consistently matched for age and duration of DM.^{8,11,16,18,20,22} Given these concerns, the results reported by Karimoei et al will be more convincing after they recalculate the association between ApoE polymorphism and DN, after age and duration of DM are adjusted.

Conflict of interest: None declared.

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References

1. Karimoei M, Pasalar P, Mehrabzadeh M, et al. Association between apolipoprotein E polymorphism and nephropathy in Iranian diabetic patients. *Saudi J Kidney Dis Transpl* 2017; 28:997-1002.
2. Gallagher H, Suckling RJ. Diabetic nephropathy: Where are we on the journey from pathophysiology to treatment? *Diabetes Obes Metab* 2016;18:641-7.
3. Al-Rubeaan K, Youssef AM, Subhani SN, et al. Diabetic nephropathy and its risk factors in a society with a type 2 diabetes epidemic: A Saudi national diabetes registry-based study. *PLoS One* 2014;9:e88956.
4. Tziomalos K, Athyros VG. Diabetic nephropathy: New risk factors and improvements in diagnosis. *Rev Diabet Stud* 2015;12:110-8.
5. Freedman BI, Bostrom M, Daeihagh P, Bowden DW. Genetic factors in diabetic nephropathy. *Clin J Am Soc Nephrol* 2007;2: 1306-16.
6. Sun YM, Su Y, Li J, Wang LF. Recent advances in understanding the biochemical and molecular mechanism of diabetic nephropathy. *Biochem Biophys Res Commun* 2013;433: 359-61.
7. Araki S. APOE polymorphism and diabetic nephropathy. *Clin Exp Nephrol* 2014;18:230-3.
8. Jiang Y, Ma L, Han C, et al. Effects of apolipoprotein E isoforms in diabetic nephropathy of chinese type 2 diabetic patients. *J Diabetes Res* 2017;2017:3560920.
9. Horita K, Eto M, Makino I. Apolipoprotein E2, renal failure and lipid abnormalities in non-insulin-dependent diabetes mellitus. *Atherosclerosis* 1994;107:203-11.
10. Eto M, Horita K, Morikawa A, et al. Increased frequency of apolipoprotein epsilon 2 allele in non-insulin dependent diabetic (NIDDM) patients with nephropathy. *Clin Genet* 1995; 48:288-92.
11. Ha SK, Park HS, Kim KW, et al. Association between apolipoprotein E polymorphism and macroalbuminuria in patients with non-insulin dependent diabetes mellitus. *Nephrol Dial Transplant* 1999;14:2144-9.
12. Liu L, Xiang K, Zheng T, et al. Co-inheritance of specific genotypes of HSPG and apoE gene increases risk of type 2 diabetic nephropathy. *Mol Cell Biochem* 2003;254:353-8.
13. Hsieh MC, Lin SR, Yang YC, et al. Higher frequency of apolipoprotein E2 allele in type 2 diabetic patients with nephropathy in Taiwan. *J Nephrol* 2002;15:368-73.
14. Satirapoj B, Supasyndh O, Dispan R, et al. Apolipoprotein E genetic polymorphisms and the development of nephropathy in type 2 diabetes. *J Med Assoc Thai* 2013;96:1119-26.
15. Atta MI, Abo Gabal K, El-Hadidi K, et al. Apolipoprotein E genotyping in Egyptian diabetic nephropathy patients. *IUBMB Life* 2016;68:58-64.
16. Boizel R, Benhamou PY, Corticelli P, et al. ApoE polymorphism and albuminuria in diabetes mellitus: A role for LDL in the development of nephropathy in NIDDM? *Nephrol Dial Transplant* 1998;13:72-5.
17. Ilhan N, Kahraman N, Seçkin D, Ilhan N, Colak R. Apo E gene polymorphism on development of diabetic nephropathy. *Cell Biochem Funct* 2007;25:527-32.
18. Erdogan M, Eroglu Z, Biray C, et al. The relationship of the apolipoprotein E gene polymorphism turkish type 2 diabetic patients with and without nephropathy. *J Endocrinol Invest* 2009;32:219-22.
19. Tien KJ, Tu ST, Chou CW, et al. Apolipoprotein E polymorphism and the progression of diabetic nephropathy in type 2 diabetes. *Am J Nephrol* 2011;33:231-8.
20. Kimura H, Suzuki Y, Gejyo F, et al. Apolipoprotein E4 reduces risk of diabetic nephropathy in patients with NIDDM. *Am J Kidney Dis* 1998;31:666-73.
21. Leiva E, Mujica V, Elematore I, et al. Relationship between apolipoprotein E polymorphism and nephropathy in type-2 diabetic patients. *Diabetes Res Clin Pract* 2007;78:196-201.
22. Joss N, Jardine A, Gaffney D, Boulton-Jones JM. Influence of apolipoprotein E genotype on progression of diabetic nephropathy. *Nephron Exp Nephrol* 2005;101:e127-33.

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