COMMENTARY

Progression of Diabetic Kidney Disease in the Absence of Albuminuria

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It has been almost 30 years since the first studies were published that challenged the concept that progression of albuminuria was an obligatory predictor of renal function loss in diabetes (1,2). Despite this and until recently, diabetic kidney disease (DKD) has been conceptualized as a condition where there is linear progression from normo- to micro- to macroalbuminuria, with this last step heralding glomerular filtration rate (GFR) loss (3,4). However, there is now a growing body of evidence to suggest that many patients with type 1 diabetes or type 2 diabetes can follow a nonalbuminuric pathway to renal function loss, even after accounting for the use of renoprotective agents (4–8).

The significance of nonalbuminuric DKD's contribution to decline in GFR and progression to end-stage kidney disease (ESKD) still remains to be fully defined. Some studies have suggested an indolent course of renal function decline for normoalbuminuric versus albuminuric DKD. Rates of GFR decline in these studies for normoalbuminuric DKD are reported to be similar to those observed in the general population of people without diabetes and similar to the expected age-related decline in GFR of approximately 1 mL/min/1.73 m^2 per year (9,10).

A study published in this issue of *Diabetes Care* (11) suggests that while the presence of albuminuria influences the rate of GFR decline in both type 1 and type 2 diabetes, with macroalbuminuric participants having the greatest decline in estimated (e)GFR, those with normoalbuminuria still display rates of renal function loss above the expected age-related decline in renal function. Furthermore, the study also shows that for participants that progressed to ESKD (eGFR $<$15 mL/min/1.73 m^2), nearly one in five did so without making the transition to macroalbuminuria.

In this study (11), eGFR trajectories were followed in 935 people with type 1 diabetes (median follow-up time 5.1 years) and 1,984 people with type 2 diabetes (median follow-up time 3.7 years) for up to 16 years after the development of chronic kidney disease (CKD) stage 3 (eGFR $<$60 mL/min/1.73 m^2). Rates of eGFR change over time were modeled over 10 years and estimated by mixed-effects models using person-specific random intercepts and slopes according to diabetes type and albuminuria status. In addition, latent class trajectory modeling was then used to define distinct eGFR patterns in people with normoalbuminuria.

For participants in the study achieving stage 3 CKD, 46% with type 1 diabetes and 48% with type 2 diabetes did so while remaining normoalbuminuric. Mean annual declines in eGFR for normo-, micro-, and macroalbuminuria following the development of CKD stage 3 were 1.9, 2.3, and 3.3 mL/min/1.73 m^2, respectively, in type 1 diabetes and 1.9, 2.1, and 3.0 mL/min/1.73 m^2, respectively, in type 2 diabetes after adjustment for numerous clinical and biochemical parameters, including the use of renin-angiotensin system (RAS)-inhibiting agents.

For normoalbuminuric participants with type 1 or type 2 diabetes, two distinct eGFR patterns were found, with one displaying an accelerated rate of eGFR decline. Interestingly, the majority of participants with type 1 diabetes (86%) experienced a 1.6 mL/min/1.73 m^2 increase in eGFR in the first year after reaching CKD stage 3, followed by a constant rate of eGFR decline (class 1 eGFR decliners). The increase possibly represented an intensification of treatment in these participants after they crossed the threshold into stage 3 CKD. In contrast, an accelerated decline in eGFR followed by a plateauing was observed in 14% of the normoalbuminuric participants (class 2 eGFR decliners); these patients had higher total cholesterol levels, took fewer lipid-modifying agents, and had higher rates of more severe retinopathy.

For participants with type 2 diabetes and normoalbuminuria, the majority (90%) followed a pattern similar to that seen in those with type 1 diabetes—that is, an initial increase in eGFR followed by

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a steady linear decline (class 1 eGFR decliners). However, in 10%, a steep eGFR decline was observed, followed by a slight increase in eGFR (class 2 eGFR decliners); these individuals exercised less, had lower blood pressure levels, and had lower use of RAS-inhibiting agents and antihypertensive and lipid-lowering medications compared to class 1 eGFR decliners.

The main strengths of the study are its longitudinal design and the use of latent class trajectory modeling, which allows a "freestyle" approach to clustering eGFR trajectory patterns without any reliance on preconceived hypotheses. It is also one of the few studies reporting on rates of change in eGFR for normalbuminuric DKD participants with type 1 or 2 diabetes attending the same facility. The main weaknesses of the study were that the participants were classified as reaching stage 3 CKD on the basis of one estimation of eGFR, direct measurements of GFR were not used, and albuminuria classification was based on one spot urinary albumin-to-creatinine ratio measurement. Furthermore, follow-up time for normoalbuminuric participants with type 2 diabetes that displayed the accelerated eGFR decline was considerably shorter than for those without this pattern of eGFR decline (2.0 vs. 4.1 years, respectively; $P = 0.027$). Also, the above patterns of eGFR trajectories may only apply to the white Danish participants who took part in this study and who were destined to reach stage 3 CKD.

While this study (11) has made an important contribution to our understanding of the significance of declining renal function in the setting of normoalbuminuric DKD, mechanistic studies remain scarce. We have previously shown that resistance of the intrarenal arteries, as estimated by the renal parenchymal resistance index, is increased in people with type 2 diabetes and impaired renal function and is increased to a similar extent regardless of albuminuric status (12). So, it is possible that increased intrarenal vascular disease contributes to declining GFR in all people with DKD and that other factors are superimposed to cause a further accelerated decline in the setting of increased albuminuria.

We and others have also shown in biopsy studies involving people with type 2 diabetes and an eGFR $<$60/mL/min/1.73 m^2 that those with normo- or microalbuminuria have fewer of the typical morphological features classically described for DKD associated with proteinuria (13,14). In contrast, classical glomerular structural changes that are typical of proteinuric DKD appear to be a common finding in normoalbuminuric people with type 1 diabetes (15). Therefore, the pathological drivers and structural basis of renal function decline in nonalbuminuric DKD still remain to be elucidated.

The results of the study by Vistisen et al. (11) support the concept that pathological declines in GFR are not uncommonly observed in normoalbuminuric people, with some even progressing to ESKD. The modification of risk factors such as dyslipidemia and hypertension in patients with declining GFR in the setting of normoalbuminuria may help to slow GFR decline. The use of sodium–glucose cotransporter 2 inhibitors is also emerging as an effective approach to slowing progression of renal function loss in people with diabetes that follow either the albuminuric or nonalbuminuric pathway to renal insufficiency (16–18).

The take-home message from this study is the importance of following eGFR as well as albuminuria trajectories in people with diabetes, an approach that has already been advocated for people with diabetes even before CKD stage 3 is reached. Previously, up to 9% of people with type 1 diabetes and 20% of those with type 2 diabetes followed by the Joslin Clinic displayed an early progressive GFR decline while remaining normoalbuminuric (19). Perhaps more importantly, the study highlights the need for new markers apart from albuminuria to identify people who are at greatest risk for the progression of normoalbumiuric DKD (20–22).

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References

1. Lane PH, Steffes MW, Mauer SM. Glomerular structure in IDDM women with low glomerular filtration rate and normal urinary albumin excretion. Diabetes 1992;41:581–586
2. Tsalamandris C, Allen TJ, Gilbert RE, et al. Progressive decline in renal function in diabetic patients with and without albuminuria. Diabetes 1994;43:649–655
3. Mogensen CE, Christensen CK, Vittinghus E. The stages in diabetic renal disease: with emphasis on the stage of incipient diabetic nephropathy. Diabetes 1983;32(Suppl. 2):64–78
4. Macisaac RJ, Jerums G. Diabetic kidney disease with and without albuminuria. Curr Opin Nephrol Hypertens 2011;20:246–257
5. Afghahi H, Miftaraj M, Svensson AM, et al.; Swedish National Diabetes Register. Ongoing treatment with renin-angiotensin-aldosterone-blocking agents does not predict normoalbuminuric renal impairment in a general type 2 diabetes population. J Diabetes Complications 2013;27:229–234
6. Porrini E, Ruggenenti P, Mogensen CE, et al.; ERA-EDTA diabesity working group. Non-proteinuric pathways in loss of renal function in patients with type 2 diabetes. Lancet Diabetes Endocrinol 2015;3:382–391
7. Molitch ME, Steffes M, Sun W, et al.; Epidemiology of Diabetes Interventions and Complications Study Group. Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications study. Diabetes Care 2010;33:1536–1543
8. Penno G, Russo E, Garofolo M, et al. Evidence for two distinct phenotypes of chronic kidney disease in individuals with type 1 diabetes mellitus. Diabetologia 2017;60:1102–1113
9. Hoefield RA, Kalra PA, Baker PG, et al. The use of eGFR and ACR to predict decline in renal function in people with diabetes. Nephrol Dial Transplant 2011;26:887–892
10. Koye DN, Magliano DJ, Reid CM, et al. Risk of progression of nonalbuminuric CKD to end-stage kidney disease in people with diabetes: the CRIC (Chronic Renal Insufficiency Cohort) Study. Am J Kidney Dis 2018;72:653–661
11. Vistisen D, Andersen GS, Hulman A, Persson F, Rossing P, Jørgensen ME. Progressive decline in estimated glomerular filtration rate in patients with diabetes after moderate loss in kidney function—even without albuminuria. Diabetes Care 2019;42:1886–1894
12. Macisaac RJ, Panagiotopoulos S, McNeil KJ, et al. Is nonalbuminuric renal insufficiency in type 2 diabetes related to an increase in intrarenal vascular disease? Diabetes Care 2006;29:1560–1566
13. Ekinci EI, Jerums G, Skene A, et al. Renal structure in normoalbuminuric and albuminuric patients with type 2 diabetes and impaired renal function. Diabetes Care 2013;36:3620–3626
14. Yamanouchi M, Furuichi K, Hoshino J, et al.; Research Group of Diabetic Nephropathy, the Ministry of Health, Labour and Welfare, and the Japan Agency for Medical Research and Development. Nonproteinuric versus proteinuric phenotypes in diabetic kidney disease: a propensity score–matched analysis of a nationwide, biopsy-based cohort study. Diabetes Care 2019;42:891–902
15. Caramori ML, Fioretto P, Mauer M. Low glomerular filtration rate in normoalbuminuric type 1 diabetic patients: an indicator of more advanced glomerular lesions. Diabetes 2003;52:1036–1040
16. Wanner C, Inzucchi SE, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323–334

17. Perkovic V, de Zeeuw D, Mahaffey KW, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. Lancet Diabetes Endocrinol 2018;6:691–704
18. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. Lancet Diabetes Endocrinol 2019;7:606–617
19. Krolewski AS, Skupien J, Rossing P, Warram JH. Fast renal decline to end-stage renal disease: an unrecognized feature of nephropathy in diabetes. Kidney Int 2017;91:1300–1311
20. Gohda T, Nishizaki Y, Murakoshi M, et al. Clinical predictive biomarkers for normoalbuminuric diabetic kidney disease. Diabetes Res Clin Pract 2018;141:62–68
21. Zoccali C, Mallamaci F. Nonproteinuric progressive diabetic kidney disease. Curr Opin Nephrol Hypertens 2019;28:227–232
22. Niewczas MA, Pavkov ME, Skupien J, et al. A signature of circulating inflammatory proteins and development of end-stage renal disease in diabetes. Nat Med 2019;25:805–813