EnM
ENDOCRINOLOGY AND METABOLISM

Editorial

Endocrinol Metab 2016;31:533-534
https://doi.org/10.3803/EnM.2016.31.4.533
pISSN 2093-596X · eISSN 2093-5978

Nonalbuminuric Renal Insufficiency: Can It Be a Novel Category of Diabetic Nephropathy?

Masami Tanaka, Hiroshi Itoh

Division of Endocrinology, Metabolism, and Nephrology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

Diabetic nephropathy is a major cause of chronic kidney disease (CKD) and a common underlying cause of hemodialysis. In order to prevent hemodialysis due to diabetic nephropathy, early detection and treatment of diabetic nephropathy are indispensable. Because the risk for cardiovascular diseases (CVDs) and treatment strategies, especially protein restriction level, differ by stage of diabetic nephropathy, an accurate evaluation of disease severity is important. In Japan, the Joint Committee on Diabetic Nephropathy revised its Classification on Diabetic Nephropathy (Classification of Diabetic Nephropathy 2014) [1]. Diabetic nephropathy is classified into five stages on the basis of albuminuria/proteinuria and estimated glomerular filtration rate (eGFR) as follows. Stage 1 (pre-nephropathy): normoalbuminuria (<30 mg/g Cr); stage 2 (incipient nephropathy): microalbuminuria (30 to 299 mg/g Cr); stage 3 (overt nephropathy): macroalbuminuria (≥300 mg/g Cr) or persistent proteinuria (≥0.5 g/g Cr); stage 4 (kidney failure): any albuminuria/proteinuria status and eGFR <30 mL/min/1.73 m^2; and stage 5 (dialysis therapy): any status on continued dialysis therapy.

Both the occurrence of albuminuria and reduction in eGFR are independent risk factors for CVD [2-4], although their clinical characteristics are somewhat different. It is accepted worldwide that albuminuria is very important biomarker of incipient diabetic nephropathy [5]. On the other hand, decline in eGFR is not useful as a diagnostic marker of incipient diabetic nephropathy [6]. Severely decreased eGFR is reported to predict renal failure or CVD regardless of the presence or absence of albuminuria [3]; therefore, it is useful as a marker of the progression of diabetic nephropathy.

Although diabetic nephropathy is classified into five stages in "Classification of Diabetic Nephropathy 2014" [1], it does not always proceed from one stage to the next orderly; there is a group of diabetic patients whose eGFR declines without the occurrence of albuminuria [7,8].

In this issue of *Endocrinology and Metabolism*, Lee et al. [9] reported that nonalbuminuric stage ≥3 CKD group (<60 mL/min/1.73 m^2) was a significant category of diabetic nephropathy, and that the patients belonging to this category showed higher prevalence of CVD and retinopathy than those with preserved eGFR (≥60 mL/min/1.73 m^2). Because this group had shorter diabetic duration than the albuminuric stage ≥3 CKD group, nonalbuminuric stage probably proceed to albuminuric stage. Since the rate of treatment with angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers of the nonalbuminuric CKD group is higher than that of the albuminuric CKD group, by treating with renin-angiotensin system antagonists, regression from albuminuric CKD to nonalbuminuric CKD might be expected.

According to the KNHANES (Korea National Health and Nutritional Examination Survey), 8.6% of diabetic patients belonged to the category of CKD defined as eGFR <60 mL/min/1.73 m^2 [10]. This proportion seemed quite low compared

Corresponding author: Masami Tanaka
Division of Endocrinology, Metabolism, and Nephrology, Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
Tel: +81-3-5363-3797, **Fax:** +81-3-3359-2745, **E-mail:** tana176k@keio.jp

with the 39% reported in this paper [9]. This discrepancy might indicate that the subjects of this retrospective study did not represent the patients observed in the real clinical settings. Although the findings of Lee et al. [9] are worthwhile from a viewpoint of early detection and intervention of the patients at high risk, a prospective study with a larger number of patients is needed to confirm and establish the significance of nonalbuminuric renal insufficiency.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Masami Tanaka *http://orcid.org/0000-0002-3759-8523*

REFERENCES

1. Haneda M, Utsunomiya K, Koya D, Babazono T, Moriya T, Makino H, et al. A new classification of diabetic nephropathy 2014: a report from Joint Committee on Diabetic Nephropathy. Diabetol Int 2014;5:207-11.
2. Drury PL, Ting R, Zannino D, Ehnholm C, Flack J, Whiting M, et al. Estimated glomerular filtration rate and albuminuria are independent predictors of cardiovascular events and death in type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetologia 2011;54:32-43.
3. Ninomiya T, Perkovic V, de Galan BE, Zoungas S, Pillai A, Jardine M, et al. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol 2009;20:1813-21.
4. Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, et al. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol 2013;24:302-8.
5. Katayama S, Moriya T, Tanaka S, Tanaka S, Yajima Y, Sone H, et al. Low transition rate from normo- and low microalbuminuria to proteinuria in Japanese type 2 diabetic individuals: the Japan Diabetes Complications Study (JDCS). Diabetologia 2011;54:1025-31.
6. Bruno G, Merletti F, Bargero G, Novelli G, Melis D, Soddu A, et al. Estimated glomerular filtration rate, albuminuria and mortality in type 2 diabetes: the Casale Monferrato study. Diabetologia 2007;50:941-8.
7. Middleton RJ, Foley RN, Hegarty J, Cheung CM, McElduff P, Gibson JM, et al. The unrecognized prevalence of chronic kidney disease in diabetes. Nephrol Dial Transplant 2006;21:88-92.
8. Hanai K, Babazono T, Nyumura I, Toya K, Tanaka N, Tanaka M, et al. Asymmetric dimethylarginine is closely associated with the development and progression of nephropathy in patients with type 2 diabetes. Nephrol Dial Transplant 2009;24:1884-8.
9. Lee HW, Jo AR, Yi DW, Kang YH, Son SM. Prevalent rate of nonalbuminuric renal insufficiency and its association with cardiovascular disease event in Korean type 2 diabetes. Endocrinol Metab 2016;31:577-85.
10. Ahn JH, Yu JH, Ko SH, Kwon HS, Kim DJ, Kim JH, et al. Prevalence and determinants of diabetic nephropathy in Korea: Korea National Health and Nutrition Examination Survey. Diabetes Metab J 2014;38:109-19.