Editorial

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The Beneficial Effect of Glycemic Control against Adverse Outcomes in Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease

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Diabetes mellitus (DM) is associated with various complications that can significantly reduce the quality of life and increase morbidity and mortality rates. Chronic kidney disease (CKD) is one of the most common diabetic complications. The prevalence of CKD is gradually increasing, which is mainly attributed to the growing number of patients with type 2 diabetes mellitus (T2DM) [1]. It has been reported that approximately 35% of patients with DM have CKD [2]. CKD has the potential to advance to end-stage renal disease (ESRD) requiring dialysis or kidney transplantation and is the most common cause of ESRD in the United States [3]. In patients with DM, CKD is significant not only because of its ability to progress to ESRD but also because of its association with other complications, particularly cardiovascular disease [4].

The main objective of managing DM is to regulate glucose levels effectively to prevent or postpone any potential complications. There have been several studies regarding the optimal target of glycemic control, and the beneficial effects of intensive glycemic control. The United Kingdom Prospective Diabetes Study (UKPDS) was conducted to evaluate the impact of intensive glycemic control in patients with T2DM. In this study, intensive glycemic control with a target glycosylated hemoglobin (HbA1c) level of 7.0% was studied with regard to microvascular complications [5]. However, there were no significant differences in microvascular complications between the intensive control and conventional control groups [5]. Subsequently, the following three randomized trials were conducted with a more stringent target of HbA1c 6.0% to 6.5%: Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial [6], Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [7], and Veterans Affairs Diabetes Trial (VADT) [8]. These studies did not demonstrate any significant positive effects of intensive glycemic control on cardiovascular disease. However, a more recently published long-term follow-up study of the UKPDS showed that the intensive control group had a lower incidence of myocardial infarction and overall death than the conventional group [9].

There is an increasing emphasis placed on individualized glycemic targets in DM [10]. Patients with DM and CKD have a higher risk of hypoglycemia than DM patients without CKD [11]. Patients with DM and CKD are more likely to be older and have other vascular complications or comorbidities compared to patients who only have DM without CKD [1]. It may be necessary to establish a different target for glycemic control in diabetic patients with CKD. The ideal target HbA1c is currently unknown for this population. The previous studies [5-9] that evaluated the impact of intensive glycemic control on diabetic complications mainly included patients with an estimated glomerular filtration rate (eGFR) of 45 mL/min/1.73 m^2 or higher. However, according to the recent guideline from Kidney Disease: Improving Global Outcomes (KDIGO), the HbA1c target was broadly suggested from <6.5% to <8.0% in patients with DM and CKD without kidney replacement therapy [12].

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In this issue of *Diabetes & Metabolism Journal*, Heo et al. [13] reported the association between glycemic control and adverse clinical outcomes in Korean patients with CKD and T2DM using data from a nationwide prospective cohort. Out of the 2,238 individuals with CKD in the original cohort, the final analysis in this study included 707 patients who also had T2DM. Patients were classified into three groups based on their HbA1c levels: <7.0%, 7.0%–7.9%, and ≥8.0%. The primary outcome was a composite of major adverse cardiovascular events (MACEs) or all-cause mortality. In this study [13], higher HbA1c levels were associated with a significantly higher risk of the composite outcome of MACE or all-cause mortality. In the time-varying Cox model, the adjusted hazard ratios (aHRs) for the primary endpoint were 1.59 (95% confidence interval [CI], 1.01 to 2.49) and 1.99 (95% CI, 1.24 to 3.19) for HbA1c levels of 7.0%–7.9% and ≥8.0%, respectively, compared with HbA1c level of <7.0%. In the secondary outcome analysis, the aHRs for the corresponding HbA1c categories were 2.17 (95% CI, 1.20 to 3.95) and 2.26 (95% CI, 1.17 to 4.37) for MACE, and 1.36 (95% CI, 0.68 to 2.72) and 2.08 (95% CI, 1.06 to 4.05) for all-cause mortality. There were no differences in the risk of adverse kidney outcomes among the three HbA1c categories.

This study did not find a significant association between HbA1c levels and the risk of CKD progression; however, according to the generalized linear mixed models, patients with an eGFR of ≥45 mL/min/1.73 m^2 showed a greater decline in eGFR with higher HbA1c levels than did those with higher eGFR. The results from this study align with previous studies, which also showed that higher HbA1c levels were more likely to progress to ESRD in patients with CKD grade 1–3 [14-16]. These findings suggest that intensive glycemic control should be prioritized in patients with early-stage CKD in order to prevent progression to ESRD.

However, there are some limitations that should be considered before generalizing this finding. As the authors pointed out, there may have been confounding factors to consider as this was an observational study. The small sample size and lack of detailed analysis about anti-diabetic medications were also limitations of this study.

Despite its limitations, this study validated the positive association between HbA1c levels and adverse clinical outcomes including MACE and mortality in Korean patients with CKD and T2DM. Based on the current findings, intensive glycemic control is recommended for this population. Further studies are needed to determine the optimal glycemic target in patients with T2DM and CKD.

CONFLICTS OF INTEREST

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

REFERENCES

1. Kim KS, Park SW, Cho YW, Kim SK. Higher prevalence and progression rate of chronic kidney disease in elderly patients with type 2 diabetes mellitus. Diabetes Metab J 2018;42:224-32.
2. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. JAMA 2011;305:2532-9.
3. Johansen KL, Chertow GM, Foley RN, Gilbertson DT, Herzog CA, Ishani A, et al. US Renal Data System 2020 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis 2021;77(4 Suppl 1):A7-8.
4. Said S, Hernandez GT. The link between chronic kidney disease and cardiovascular disease. J Nephropathol 2014;3:99-104.
5. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.
6. ADVANCE Collaborative Group; Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560-72.
7. Action to Control Cardiovascular Risk in Diabetes Study Group; Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-59.
8. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129-39.
9. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.
10. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 6. Glycemic targets: standards of care in diabetes-2023. Diabetes Care 2023;46(Suppl 1):S97-110.
11. Moen MF, Zhan M, Hsu VD, Walker LD, Einhorn LM, Seliger

SL, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. Clin J Am Soc Nephrol 2009;4:1121-7.
12. Navaneethan SD, Zoungas S, Caramori ML, Chan JC, Heerspink HJ, Hurst C, et al. Diabetes management in chronic kidney disease: synopsis of the 2020 KDIGO clinical practice Guideline. Ann Intern Med 2021;174:385-94.
13. Heo GY, Koh HB, Kim HW, Park JT, Yoo TH, Kang SW, et al. Glycemic control and adverse clinical outcomes in patients with chronic kidney disease and type 2 diabetes mellitus: results from KNOW-CKD. Diabetes Metab J 2023;47:484-6.
14. Shurraw S, Hemmelgarn B, Lin M, Majumdar SR, Klarenbach S, Manns B, et al. Association between glycemic control and adverse outcomes in people with diabetes mellitus and chronic kidney disease: a population-based cohort study. Arch Intern Med 2011;171:1920-7.
15. Liao LN, Li CI, Liu CS, Huang CC, Lin WY, Chiang JH, et al. Extreme levels of HbA1c increase incident ESRD risk in Chinese patients with type 2 diabetes: competing risk analysis in national cohort of Taiwan Diabetes Study. PLoS One 2015;10:e0130828.
16. Oh SW, Kim YC, Koo HS, Jin DC, Na KY, Chae DW, et al. Glycated haemoglobin and the incidence of end-stage renal disease in diabetics. Nephrol Dial Transplant 2011;26:2238-44.