How much glycemic control is needed to prevent progression of diabetic nephropathy?

Last year, the International Diabetes Federation released new figures showing that the number of people living with diabetes worldwide is expected to rise from 366 million in 2011 to 552 million by 2030. This equates to approximately three new cases every 10 s, and one adult in 10 will have diabetes by 2030[1]. Unexpected rapid increases of diabetic patients in developing and developed countries, and the global burden of chronic kidney disease (CKD) is expected to increase dramatically within coming decades.

Diabetes mellitus is the major cause of end-stage renal disease (ESRD) throughout the world, in both developed and under-developed countries. Diabetic nephropathy is the primary diagnosis causing CKD in 40–50% of newly developed ESRD patients worldwide. These patients experience a low quality of life, and a high hospitalization and mortality rate. Approximately two-thirds of ESRD patients with dialysis die within 5 years of initiation of dialysis treatment, and 5-year survival is worse than that expected in the majority of patients with cancer[2].

Diabetic nephropathy does not develop in all diabetic patients and it is believed to be a progressive disease from microalbuminuria to macroalbuminuria and ESRD. The diagnosis of diabetic nephropathy can be made in diabetic patients by the persistent presence of albumin in the urine, or continuous rise in serum creatinine, or a reduction in the glomerular filtration rate. However, many diabetic patients will not show microalbuminuria before experiencing a decline in their renal function[3]. The progression to advanced CKD and ESRD usually occurs over years, although not all patients follow this course. Therefore, a strategy to detect diabetic kidney disease earlier by screening for albuminuria and reduced glomerular filtration rate is important to prevent progression of diabetic nephropathy.

Fortunately, there is evidence that early therapeutic intervention in diabetic patients with CKD can delay the onset of complications and improve outcomes. Several studies suggest that the incidence and progression of diabetic neuropathy is consistently reduced in diabetic patients with tight glycemic control (glycated hemoglobin [HbA$_{1c}$] <7% or lower). Action in Diabetes and Vascular disease: PreterAx and DiamicroN-MR Controlled Evaluation (ADVANCE), Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Veterans Affairs Diabetes Trial (VADT) have shown a significant reduction in new or worsening nephropathy, and progression to macroalbuminuria in high-risk patients with type 2 diabetes assigned to an intensive glucose-control strategy. Combined data from these three trials have shown similar hazard ratios with 95% confidence intervals in a similar range (relative risk ratio: 0.64–0.79). Although previous studies have suggested that the effect of glycemic control on morbidity and mortality in patients with normal kidney function and with early stages of diabetic nephropathy is effective, recent clinical trials have provided conflicting results on tight glycemic control outcomes in patients with advanced CKD or ESRD. In VADT, despite the reduced progression of albuminuria, the intensive glycemic control had no significant effect on the doubling of serum creatinine level or glomerular filtration rate <15 mL/min for 5.6 years of median follow up. Similarly, in a follow-up study of the ACCORD trial, the outcome of ESRD was not significantly different between the intensive and standard glucose control groups.

Shurraw et al.[4] determined whether HbA$_{1c}$ level is independently associated with important clinical outcomes, such as all-cause mortality, cardiovascular events, hospitalizations and kidney failure, in people with diabetes mellitus and stage 3–4 CKD. They reported that a higher HbA$_{1c}$ (>9%) in diabetic CKD patients was associated with markedly worse clinical outcomes, and lower HbA$_{1c}$ (<6.5%) was associated with excess mortality. They emphasized the importance of a high HbA$_{1c}$ level as a risk factor for renal outcomes and that prudent practice was required for moderately intensive risk factor management while minimizing the potential for serious adverse effects of the treatment regimens. In conclusion, they suggested that appropriate and timely control of fasting and postprandial glucose, and HbA$_{1c}$ level in people with diabetes mellitus and CKD might be more important than previously realized. Oh et al.[5] retrospectively assessed the appropriate HbA$_{1c}$ level for diabetics to minimize the incidence of ESRD and all cause mortality. They reported that HbA$_{1c}$ <6.5% was associated with reduced development of ESRD in all patients and later stages of CKD compared with HbA$_{1c}$ ≥6.5%, regardless of glomerular filtration rate. However, HbA$_{1c}$ <6.5% showed no benefit on ESRD development in patients older than 80 years and in patients with diabetic duration >10 years.

As a result of these studies, a HbA$_{1c}$ target of 7.0% is appropriate for the majority of patients with diabetic nephropathy (Table 1). A lower target will increase their risk of hypoglycemia and might increase their risk of mortality, whereas a higher target might accelerate the rate at which renal failure and other diabetes complications develop. The selection of the optimal HbA$_{1c}$ needs to be individualized for each patient by considering the variables, such as patient characteristics, treatment modalities, and relative risks and benefits of different levels of glycemia.

Table 1 | Target glycated hemoglobin in chronic kidney disease by National Kidney Foundation/Kidney Disease Outcomes Quality Initiative classification in diabetic patients

Stage	Description	GFR (mL/min/1.73 m^2) for ≥3 months	Target HbA$_{1c}$
1	Normal or ↑ GFR	>90	≤7%
2	Mild ↓ GFR	60–89	≤7%
3	Moderate ↓ GFR	30–59	≤7%
4	Severe ↓ GFR	15–29	≤7%
5	Kidney failure	<15 or dialysis	>7% (?)

GFR, glomerular filtration rate; HbA$_{1c}$, glycated hemoglobin.

It is unclear, however, what therapeutic target level marker has to be used for glycemic control in advanced CKD and ESRD patients, and in what stages of CKD its application has to replace or supplement HbA$_{1c}$, which could be confounded in the uremic milieu. To avoid of the drawbacks of HbA$_{1c}$, the use of fructosamine and glycated albumin in long-term glycemic control in advanced CKD patients has been proposed, but they are not superior to HbA$_{1c}$ in ESRD patients[2]. Therefore, we have to use other adequate methods, such as a continuous glucose monitoring system, to measure glycemic variability.

Until now, the optimal glycemic control in patients with advanced CKD had not been determined. The American Diabetes Association and National Kidney Foundation both recommend achieving a HbA$_{1c}$ level of 7.0% in most patients with diabetes, regardless of the presence of CKD. The issue of long-term outcomes as a function of diabetes control is especially complicated in patients with advanced CKD and ESRD in whom there are complex changes affecting glucose homeostasis[2]. The gradual decline in renal function in itself causes significant changes that alter glucose homeostasis in patients with diabetic kidney disease. The reasons for these alterations in glucose homeostasis are multifactorial and involve various mechanisms related to both decreased renal function. Once glomerular filtration rate declines below 15–20 mL/min, the renal and hepatic clearance of insulin decreases significantly. Counterbalancing diminished insulin clearance is lower insulin production and increased insulin resistance. It is also unclear what the ideal target HbA$_{1c}$ level has to be for glycemic control in diabetic ESRD patients. The advantages of a normal blood sugar level in advanced CKD and ESRD likely take a very long time to manifest, and in the short-term these patients might in fact be more prone to developing clinically relevant hypoglycemic episodes. Observational studies in ESRD patients indeed suggest that patients with the lowest HbA$_{1c}$ levels suffer significantly higher mortality rates. Recent studies in patients with normal kidney function, but advanced diabetes, showed that attempts to improve blood glucose control toward levels resembling normoglycemia can become deleterious, possibly because of the consequences of hypoglycemic events.

The effect of optimal blood glucose control on outcomes in patients with advanced CKD and ESRD is less well-studied, with a limited number of published studies showing somewhat inconsistent results. Therefore, larger clinical trials are required to show that that better glycemic control is beneficial in patients with advanced CKD and ESRD, and most importantly to establish what an ideal blood glucose level is in these patients. Hyperglycemic patients with advanced CKD and ESRD are usually treated in clinical practice based on guidelines established for patients with normal kidney function. Although this is probably better than not treating them at all, more practical efforts are required to ensure that the undesirable complications of over-enthusiastic therapy are avoided and to find suitable criteria for advanced CKD and ESRD patients.

In conclusion, recently, diabetes prevalence has increased in developed and underdeveloped countries. The number of diabetic kidney disease patients has increased very rapidly, and their economic burden for management of advanced CKD and ESRD has become a significant problem for individual patients and society. Therefore, earlier detection of diabetic nephropathy patients is essential for preventing the progression to advanced CKD and ESRD; and, optimal glycemic control for early diabetic nephropathy patients is required as an effective strategy in preventing and delaying the development of CKD. Up to the present, we do not have an optimal glucose control level and HbA$_{1c}$ level for advanced CKD and ESRD patients in clinical practice guidelines. In addition, we don't have adequate therapeutic target markers for monitoring glycemic control in diabetic dialysis patients. Therefore, we must carry out large clinical trials to determine the proper glucose level and HbA$_{1c}$ for advanced CKD and ESRD patients to decrease the hospitalization rate, increase survival time and improve the quality of life.

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