Comprehensive risk management of diabetic kidney disease in patients with type 2 diabetes mellitus

Shin-ichi Araki¹

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Abstract

Diabetic kidney disease (DKD) in patients with type 2 diabetes mellitus is a leading cause of end-stage renal disease worldwide. An increase in the severity of albuminuria and a decrease in the glomerular filtration rate, by which the DKD stages are categorized, are associated with higher risks of not only end-stage renal disease but also all-cause mortality and cardiovascular mortality. Thus, an optimal management strategy and adequate assessment of therapeutic success are of great clinical and societal relevance to improve the prognosis in patients with type 2 diabetes mellitus and DKD. At present, comprehensive risk management for glycemia, blood pressure, lipid profile, and lifestyle habits is emphasized with respect to cardio-renal protection, rather than one single risk management approach. However, the pharmacological therapy aiming at strict control of these risk factors may be associated with an increased risk of adverse effects, particularly in older adults with diabetes. Accordingly, in the clinical practice of diabetes care, we need to individualize the treatment goals for each risk factor according to the health and social status of each patient with type 2 diabetes mellitus and DKD.

Keywords Type 2 diabetes mellitus · Diabetic kidney disease · Albuminuria · Comprehensive risk management · Multifactorial intervention · Remission

Introduction

Diabetic kidney disease (DKD) in patients with type 2 diabetes mellitus is a leading cause of end-stage renal disease (ESRD) worldwide. According to an annual survey of regular dialysis treatment in Japan, the population on dialysis at the end of 2016 exceeded 320,000 patients, among which 38.4% of the cases were attributed to diabetes [1]. Another practical aspect of DKD is its association with increased risks of cardiovascular morbidity and mortality. An increase in the severity of albuminuria and a decrease in the glomerular filtration rate (GFR), by which the DKD stages are categorized, are closely associated with higher risks of all-cause mortality and cardiovascular mortality [2, 3]. Thus, the management of DKD is an important therapeutic objective to extend the healthy lifespan and maintaining the quality of life of the patients, which are the treatment goals of diabetes care. The appropriate management strategy and

adequate evaluation of treatment success in patients with type 2 diabetes mellitus and DKD are of great clinical and societal relevance to improve the prognosis.

Heterogeneity in the natural history of DKD

In the typical natural history of DKD, an elevated urinary albumin excretion, referred to as microalbuminuria, is considered the initial manifestation of the disease process. Then, this gradual increase in albuminuria progresses to overt proteinuria, a rapid worsening in the renal function, and eventually to ESRD [4]. In this typical process, DKD is considered to gradually progress from one stage to the next. However, recently, growing evidence has provided new insights, suggesting that this disease process presents in a more heterogeneous manner and does not always progress from one stage to the next.

Since the concept of chronic kidney disease (CKD) was first proposed in the early 2000s [5], the estimated GFR (eGFR) has been widely used in clinical practice to conveniently assess renal function. Using the eGFR as a measurement of renal function, several cross-sectional studies have

✉ Shin-ichi Araki
araki@belle.shiga-med.ac.jp

¹ Department of Medicine, Shiga University of Medical Science, Otsu, Shiga 520-2192, Japan

revealed that a subset of patients with type 2 diabetes mellitus and normoalbuminuria already present a loss of renal function, defined as an eGFR of less than 60 ml/min/1.73 m² [6–8], although those with normoalbuminuria were previously considered to have normal renal function. Furthermore, the proportion of patients showing discrepancy with the classification of DKD stages has been recently increasing. Among the US adults with diabetes, the overall prevalence of DKD from 1988 to 2014 did not change, whereas the prevalence of albuminuria decreased progressively over time and the prevalence of reduced eGFR increased [9]. This trend is also observed in Japanese patients with type 2 diabetes mellitus who have been enrolled in our Shiga Prospective Observational Follow-up Study [10]. The rates of patients with eGFR less than 60 ml/min/1.73 m² among those with normoalbuminuria enrolled from 1996 to 1997 and from 2006 to 2007 were 5.4 and 18.1%, respectively (Fig. 1).

Moreover, there is growing evidence that there has been a reduction in albuminuria, both from observation studies [11–13] and post hoc studies of intervention trials [14–16].

Fig. 1 Distribution of Japanese patients with type 2 diabetes according to the eGFR and urinary AER. Red diamonds indicate patients enrolled from 1996 to 1997 ($n = 645$). Among them, the rates of those with eGFR less than 60 ml/min/1.73 m² in each albuminuria category were 5.4% in normoalbuminuria ($n = 367$), 11.1% in microalbuminuria ($n = 189$) and 55.1% in overt proteinuria ($n = 89$). Black closed circles indicate patients enrolled from 2006 to 2007 ($n = 458$). Among them, the rates of those with eGFR less than 60 ml/min/1.73 m² in each albuminuria category were 18.1% in normoalbuminuria ($n = 299$), 31.5% in microalbuminuria ($n = 124$) and 57.1% in overt proteinuria ($n = 35$). The blue dotted line indicates eGFR 60 ml/min/1.73 m². The albuminuria categories were classified as normoalbuminuria if the AER (µg/min) was < 20, microalbuminuria if $20 \leq \text{AER} (\mu\text{g/min}) < 200$, and overt proteinuria if the AER (µg/min) was ≥ 200 based on the levels of urinary AER in the 24-h urine collection. AER albumin excretion rate, eGFR estimated glomerular filtration rate

These findings indicate that these two measures, albuminuria and GFR, are not always closely coupled to the prognosis of DKD and, particularly, the changes in albuminuria appear very dynamic and reversible. These insights may result from the current improvement of diabetes care. Notably, the widespread use of renin–angiotensin system (RAS) blockers, which are first-line antihypertensive drugs in diabetic patients with albuminuria, has contributed to the reduction in albuminuria. With such progression in this field, the prevalence of all diabetic complications actually declined between 1990 and 2010 in the United States, with relative declines in acute myocardial infarction, death from hyperglycemic crisis, stroke, amputations, and ESRD of 67.8, 64.4, 52.7, 51.4, and 28.3%, respectively [17].

Corresponding with these current changes surrounding DKD, the Joint Committee on Diabetic Nephropathy in Japan, which was established by the Japan Diabetes Society, Japanese Society of Nephrology, Japanese Society for Dialysis Therapy, and Japan Society of Metabolism and Clinical Nutrition, has revised its classification of DKD (Classification of Diabetic Nephropathy 2014) to resolve the discrepancy between the existing classification of DKD and the current classification of CKD stages [18]. In this revised classification, it is stressed that DKD does not always progress from one stage to the next.

Comprehensive risk management for DKD prevention

To delay the development and progression of DKD, the importance of strict control of glycemia [19, 20] and blood pressure (e.g., through the use of RAS blockers) [21–23] has been demonstrated by numerous clinical trials conducted from the 1990s to the early 2000s. However, these trials also revealed that strict control of only one risk factor is insufficient to completely prevent the development of DKD, since numerous clinical and pathological factors are involved in its disease process, and most patients with DKD have several concomitant risk factors. Thus, comprehensive risk management of glycemia, blood pressure, lipid profile, body weight, and lifestyle habits by a diabetes specialist team is emphasized by numerous clinical guidelines for diabetes care.

The beneficial effect of comprehensive risk management for preventing the progression of DKD has been demonstrated by the Steno-2 study. This study was conducted to compare the effect of a targeted, intensified, multifactorial intervention on modifiable risk factors for cardiovascular disease with that of conventional treatment in patients with type 2 diabetes and microalbuminuria. Eighty patients each were randomly assigned to receive conventional treatment in accordance with the national guidelines or intensive treatment by the diabetes care team at the Steno Diabetes Center,

with a stepwise implementation of behavior modification and pharmacologic therapy that targeted hyperglycemia, hypertension, dyslipidemia, and so on. During the mean follow-up of 7.8 years, multifactorial risk management reduced the risk of progression of nephropathy by approximately 60% [24]. In addition, patients receiving multifactorial risk management had significantly lower risks of macrovascular complications [24] and mortality [25]. Furthermore, risk reductions for all-cause mortality and ESRD were observed over 21.2 years of follow-up in the subjects originally assigned to the multifactorial treatment group, while patients in the original conventional therapy group started intensified treatment with identical targets during the follow-up period [26, 27]. The effect for mortality was associated with a 7.9-year longer median lifespan, which was matched by the time free from incident cardiovascular disease [26]. These long-term beneficial effects of intensive care at the early stage are often called ‘metabolic memory’ or ‘legacy effect’. Similarly, Joss et al. demonstrated that an intensive treatment slowed the progression of renal disease in patients with type 2 diabetes and DKD, defined as albuminuria > 300 mg/24 h, in a 2-year prospective randomized-controlled study comparing intensive medical management with standard care [28]. From this result, the authors estimated that the onset of dialysis would be delayed by 20 years in the intensive group compared with the control group, assuming that the rates of progression achieved at the end of the study persisted [28].

Comprehensive risk management has also been reported to be beneficial for the prevention of the onset of microalbuminuria. Tu et al. investigated the effect of tightly controlling multiple factors recommended as targets by the American Diabetes Association (HbA_{1c} < 7%, systolic blood pressure < 130 mmHg, and high-density lipoprotein (HDL) cholesterol > 40 mg/dl for men and > 50 mg/dl for women) on the development of new-onset of microalbuminuria in a 4.5-year longitudinal cohort of 1290 Chinese patients with type 2 diabetes and normoalbuminuria [29]. They found a strong association between the simultaneous control of multiple American Diabetes Association-recommended target factors during the study period and a decreased risk of the onset of microalbuminuria. On the contrary, the ADDITION-Europe Study did not reveal significant risk reductions in microvascular events by intensive multifactorial treatment compared with routine care in over 2000 people with type 2 diabetes newly detected by screening [30]. In this study, newly identified patients with type 2 diabetes were followed for 2 years and, consequently, their rates of onset and progression of albuminuria were found to be lower than those of the previous reports. These lower rates may be one reason for why this study did not show a difference between the two groups.

What about the effect of comprehensive risk management by a diabetes care team in patients with advanced DKD? Chan et al. demonstrated that, among 205 Chinese patients

with type 2 diabetes and renal insufficiency, receiving protocol-driven care delivered by a diabetes specialist team resulted in the patients being more likely to attain multiple treatment targets, which was associated with a reduced risk of the 2-year incidence of death and/or ESRD compared to those receiving usual care [31]. Fogelfeld et al. also revealed that a proof-of-concept multifactorial-multidisciplinary intervention by a diabetes care team showed promise in reducing the 2-year incidence of ESRD in comparison to usual care among patients with type 2 diabetes and CKD stages 3–4 [32]. Taken together, these studies indicate that comprehensive risk management by a diabetes care team contributes to delaying or preventing the progression of DKD.

Strategy for remission/regression of DKD

Only a few decades ago, the disease progress of DKD was considered progressive and irreversible. However, recent studies have demonstrated that this process is able to not only be delayed, but also reversed, by adequate management. A landmark study of this concept was reported by Fioretto et al. [33]. They demonstrated that a 10-year normalization of blood glucose levels by pancreas transplantation in patients with type 1 diabetes mellitus made it possible to reverse the typical glomerular and tubulointerstitial lesions observed at the time of transplantation. In addition, numerous randomized trials in patients with type 2 diabetes mellitus, which investigated the effects of RAS blockers, have reported a significant reduction in urinary albumin excretion [21–23]. Subsequently, several observational studies and post hoc studies of randomized trials have reported that remission of microalbuminuria/overt proteinuria was frequently observed in patients with type 2 diabetes mellitus [11–16]. Furthermore, regarding the clinical benefits of a reduction in albuminuria, there are several reports showing that a reduction in albuminuria, regardless of whether it is spontaneous or treatment-induced, associates with not only a decreased rate of GFR decline [13, 14, 34, 35], but also a low incidence of cardiovascular complications [35–38].

For example, our observational study in 216 Japanese patients with type 2 diabetes and microalbuminuria showed that the 6-year cumulative incidence of remission, defined as a shift from microalbuminuria to normoalbuminuria, and the rate of a reduction in albuminuria of more than 50% from baseline was 51 and 54%, respectively, whereas that of progression, defined as a shift from microalbuminuria to overt proteinuria, was 28% [11]. Furthermore, accumulation of the number of factors achieved at the treatment goal (HbA_{1c} < 6.9%, blood pressure < 130/80 mmHg, and total cholesterol < 200 mg/dl; triglycerides < 150 mg/dl; and HDL cholesterol > 40 mg/dl) recommended by the

Japanese Diabetes Society at that time was associated with an increased likelihood of remission of microalbuminuria [11]. To explore the subsequent clinical impact from the reduction of microalbuminuria, we expanded the follow-up by a 2-year period beyond our previous study [11], for a total 8-year follow-up period after the initial evaluation period, and investigated whether changes in microalbuminuria translated into changes in the renal and cardiovascular risk [35]. The adjusted risk for the composite outcome of renal and cardiovascular events in subjects after remission (remission group) was 0.25 [95% confidence interval (CI) 0.07–0.87] in comparison to those whose microalbuminuric stage did not change during the follow-up (no change group), while that after progression (progression group) was 2.55 (95% CI 1.04–6.30). In addition, the annual decline rate of eGFR in the progression group (median -4.2 ml/min/1.73 m²/year) was significantly faster than in the no change group (-2.4 ml/min/1.73 m²/year), whereas the annual decline rate of eGFR in the remission group was significantly slower (-1.1 ml/min/1.73 m²/year). These results suggest that optimal control of multifactorial risks is effective for inducing remission/regression of microalbuminuria as opposed to the control of only one single risk factor, and that the treatment goals for glycemia, blood pressure, and lipid profile recommended by the current clinical guidelines seem to be clinically reasonable for the reduction in albuminuria. In addition, reducing albuminuria may be clinically used as a biomeasure of therapeutic success in patients with type 2 diabetes and albuminuria.

Taken together with these previous results, albuminuria is considered to be one of the most important clinical indicators to predict the prognosis in patients with type 2 diabetes. An important question is how often albuminuria is quantitatively measured in the real world. The Shiga Medical Association has carried out the Shiga Diabetes Clinical Survey to investigate the status of diabetic medical performance in Shiga prefecture, located in the central part of Japan. Until now, three cross-sectional data collections, performed in 2000, 2006, and 2012, have been analyzed [39]. In this survey, we asked whether the quantitative measurement of urinary albumin excretion in each patient with diabetes was examined within 1 year. As a result, the proportions of patients who were examined for the measurement of albuminuria at least once was 20.7% in 2000, 27.2% in 2006, and 37.2% in 2012 [39]. The measurement of albuminuria has been gradually increasing over the 12 years, but over half of all patients with diabetes in Shiga prefecture have not undergone any examination of albuminuria. This means that over half of patients with diabetes are not aware of whether they have DKD, and have lost the opportunity to receive optimal treatment for improving the prognosis. Thus, the quantitative measurement of urinary albumin excretion for early detection of DKD and, subsequently, starting adequate

treatment promptly, should be performed in patients with type 2 diabetes mellitus at the initial visit and annually thereafter, as appropriate.

What is the optimal treatment goal for each risk factor?

As mentioned above, the treatment goals for the risk factors recommended by the current clinical guidelines seem to be reasonable for ensuring risk reduction of the progression of DKD. Recently, the exciting results of J-DOIT3 [40], a randomized study conducted to investigate the effectiveness and safety of a more intensive multifactorial intervention for glycemia, blood pressure, and low-density lipoprotein (LDL) cholesterol than the current targets in Japanese guideline [41], have been reported. This study was an open label, randomized, parallel-group trial that enrolled a total of 2542 Japanese patients with type 2 diabetes mellitus. Notably, the number of participants in this trial was more than 10 times larger than that in the Steno-2 study. In this trial, the participants were randomly assigned to intensive therapy [targets of HbA1c < 6.2%, blood pressure < 120/75 mmHg, LDL cholesterol < 80 mg/dl (or 70 mg/dl in patients with a history of coronary artery disease)] or conventional therapy. During a mean follow-up of 7.8 years, intensive therapy tended to associate with a lower risk of the primary endpoint (a composite of myocardial infarction, stroke, revascularization, and all-cause mortality), without an increased incidence of severe adverse events; however, it did not reach statistical significance [hazard ratio (HR) 0.81, 95% CI 0.63–1.04]. On the other hand, the risk of onset or progression of nephropathy was significantly reduced (HR 0.68, 95% CI 0.56–0.82). One plausible reason why intensive therapy did not show a clear benefit in the primary outcome in this trial may be due to the low incidence of the outcome even in the conventional therapy group. The incidences of macrovascular complications and cardiovascular mortality in this trial were only approximately half of those observed in the JDCS trial [42] started 10 years before J-DOIT3; this may reflect the improvement of diabetes care, as the authors discussed. Taken together, the results of J-DOIT3 suggest that more intensive management of multifactorial risks compared to the treatment goals recommended by the current guidelines could lead to cardio-renal prevention, with no significant increase in severe adverse effects of the medications.

However, it is not easy to achieve and maintain strict control of these factors in clinical practice. The Japan Diabetes Clinical Data Management (JDDM) Study Group, which consists of 17 Japanese general practitioners specializing in diabetes care, reported that 52.9% of 9956 Japanese patients with type 2 diabetes achieved HbA1c less than 7.0%, 46.8% achieved blood pressure less than 130/80 mmHg, and 65.5%

achieved the recommended target levels for the lipid profile; consequently, only 20.8% of patients met all three treatment targets, whereas 11.8% achieved none of the targets [43]. This large-scale survey indicated that the achievement ratio of all three recommended targets is insufficient in clinical practice.

In addition, J-DOIT3 did not include elderly patients over 70 years old. The number of older adults with diabetes is progressively increasing with the accelerated aging of society worldwide [39, 44]. There is no evidence that using medications to achieve intensive control of hyperglycemia, hypertension, and dyslipidemia in older adults with diabetes is beneficial. On the contrary, these intensive targets in older adults with diabetes may even be potentially harmful. In particular, severe hypoglycemia not only impairs cognitive function [45] but can also increase the risk of cardiovascular events [46, 47]. Recurrent hypoglycemia in older adults with diabetes may be a marker of vulnerability [48]. Thus, the current clinical guidelines for older adults with diabetes provide a consensus framework for considering the treatment goals for glycemia, blood pressure, and lipid profile according to their health status [49–51]. In these frameworks, the treatment goals for risk factors in older adults with diabetes are recommended to be individualized taking into consideration the individual's overall health, comorbidity of vascular complications, physical activity, cognitive function, and expected longevity. In particular, the pharmacological interventions should be carefully reviewed according to each patient's needs, and severe adverse effects of the medications, such as severe hypoglycemia, hypotension, and hyperkalemia [52], should be avoided.

New treatments for cardio-renal prevention

It is a fact that the current improvement of diabetes care is leading to improved survival and renal prognosis [17, 53], and recent developments of medications for diabetes care have largely contributed to this improvement. Recently, there is emerging evidence that sodium-glucose cotransporter 2 (SGLT2) inhibitors have a protective effect for DKD and macrovascular complications independent of diabetes control. Especially, two randomized trials, the EMPA-REG outcome trial and CANVAS Program, provided interesting evidence in this field [54, 55]. In the EMPA-REG outcome trial, a total of 7020 patients with type 2 diabetes mellitus at high risk for cardiovascular diseases were assigned to receive empagliflozin or a placebo [54]. The primary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The renal composite outcome included doubling creatinine, renal replacement therapy, or renal death. During a median follow-up of 3.1 years,

patients who received empagliflozin when SGLT2 inhibitors were added to the standard care had a significantly lower rate of the primary composite cardiovascular outcome (HR 0.86, 95% CI 0.74–0.99), as well as of the renal composite outcomes, compared with the placebo group [56].

Consistent with the results of the EMPA-REG outcome trial, the CANVAS Program tested another SGLT-2 inhibitor, canagliflozin, and reported beneficial effects of this drug on the cardiovascular and renal outcomes [55]. The CANVAS Program involved a total of 10,142 participants with type 2 diabetes and established cardiovascular disease or at high risk for cardiovascular events who were randomly assigned to receive canagliflozin or a placebo. The primary outcome in this trial was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. During a mean of 188.2 weeks, patients who were treated with canagliflozin had significantly lower rates of the primary cardiovascular outcome than patients assigned to receive the placebo (HR 0.86, 95% CI 0.75–0.97). As well, this trial showed the possible benefit of canagliflozin on renal outcomes, including the progression of albuminuria (HR 0.73, 95% CI 0.67–0.79) and the composite outcome of a sustained 40% reduction in the eGFR, the need for renal replacement therapy, or death from renal causes. Thus, the beneficial effect of SGLT2 inhibitors on cardio-renal protection appears promising and is likely a class effect.

Why do SGLT2 inhibitors, but not other glucose-lowering medications, show a beneficial effect on cardio-renal protection? The exact mechanism remains unclear, although numerous plausible hypotheses have been proposed [57, 58]. The principle pharmacological action of SGLT2 inhibitors is to inhibit the proximal tubular reabsorption of glucose filtered through the glomerulus. Subsequently, enhanced glycosuria leads to lower blood glucose levels and reduced body weight. Moreover, SGLT2 inhibitors have not only antihyperglycemic effects but also osmotic and natriuretic effects, resulting in a decrease in blood pressure, reduced uric acid levels, increased hematocrit, and so on. In particular, reducing the intraglomerular pressure and protecting the renal proximal tubular hypoxia by SGLT2 inhibition may be beneficial for improving renal outcomes [59]. These multifactorial metabolic and hemodynamic effects in addition to the lowering of hyperglycemia most likely contribute to cardio-renal protection cooperatively. In other words, the use of SGLT2 inhibitors may result in identical effects as multifactorial risk management by one medication. Thus, the results of these trials using SGLT2 inhibitors strongly support the concept that comprehensive risk management is crucial for cardio-renal protection, rather than management of a single risk factor.

Conclusion

Comprehensive risk management is beneficial to extend the healthy lifespan and to maintain quality of life in patients with type 2 diabetes and DKD. Prompt initiation of this approach at the early stage of DKD seems to be better for reducing the future incidence of ESRD and cardiovascular complications. Thus, physicians need to regularly measure the urinary albumin excretion and eGFR to identify patients at risk, and should longitudinally assess the changes of these markers as biomeasures of the therapeutic success. However, the practice of comprehensive risk management aiming at the strict control of risk factors may be associated with an increased risk of adverse effects from the medications such as hypoglycemia, particularly in older adults. In addition, it is a fact that a substantial residual risk is still present, despite optimal treatment recommended by the current clinical guidelines. Therefore, we need to individualize the treatment goal for each risk factor according to the health and social status of each patient and develop new drugs targeting the pathological pathways involved in the development of DKD.

Compliance with ethical standards

Ethical approval The Shiga Prospective Observational Follow-up Study was approved by the local ethics committee of the Shiga University of Medical Science (approval number: 2, approval date: 1 February 1996), and was conducted in accordance with the principles of the Helsinki Declaration.

Conflict of interest The author declares no conflict of interest.

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