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COMMENT

New insights regarding clinical goals for preventing rapid decline in renal function in Japanese population

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Chronic kidney disease, (CKD) which affects roughly 700 million individuals of the general population worldwide, emerges as a major public concern [1]. Not only is CKD the eighth leading cause of death in Japan, but CKD is also linked to high prevalence of cardiovascular disease (CVD). With an increase in the number of Japanese population with CKD, the medical expenses have currently been rising, which places a financial burden on the Japanese government. Thus, a multi-pronged approach such as raising awareness of CKD, detecting patients with CKD at early stage, and providing a comprehensive treatment, is underway to prevent progression of CKD. The comprehensive treatment for patients with CKD includes managing dietary intake of sodium [2], lowering blood pressure [3], reducing blood glucose [4] and low-density lipoprotein cholesterol [5], and preventing obesity [6]. However, even considering blood pressure, only about half of the patients achieved therapeutic goal which is less than 130/80 mmHg for patients with diabetes and CKD [7]. Thus, the information regarding clinical background of the patients who declines renal function rapidly would be of great importance for nephrologists. Since the racial difference has an impact on the clinical outcome, the insights and knowledge of the therapeutic goals derived from Japanese population will help better understand how to slow the progression of CKD.

Fujii et al. demonstrated that rapid decline in renal function is associated with high systolic blood pressure (sBP), poor glycemic control, increased urinary protein excretion, and decreased hemoglobin in general population aged between forty to seventy-four [8]. They analyzed the large volume data of overall 3,673,829 national-wide population collected from Japanese check-up system. A subgroup analysis was performed to determine what clinical parameter affects the rapid decline in renal function in patients with or without diabetes mellitus. They defined the estimated GFR (eGFR) decline in >–10% per year as a rapid decline in renal function, and found that relative risk of rapid decline in renal function was gradually increased when sBP raises from 120 mmHg. In the case of over 160 mmHg, the relative risk increased by 37%–54% regardless of the diabetic status. The patients of 120–130 mmHg showed the significant increase in the risk of rapid decline in renal function; but the increase rate was relatively low (Odds ratio, 1.10; 95% CI, 1.07 to 1.13), which allows us to consider that controlling <125 mmHg, the therapeutic goal of home sBP proposed by Japanese Society of Nephrology for the patients with CKD having >1 g proteinuria, is reasonable for avoiding the risk of rapid decline in renal function in patients with CKD. It is generally accepted that angiotensin II converting enzyme inhibitor (ACE-I) or angiotensin II type 1 receptor blocker (ARB) is the first-line agent not only to lower sBP but also to reduce intraglomerular pressure and inhibit CKD progression. Even if treatment with ACE-I/ARB causes a tentative drop in eGFR, they are shown to prevent the progression of CKD from the view of long-term period. Consistent with previous studies [9], Fujii et al. demonstrated that the risk for rapid decline in renal function was elevated with an increase in proteinuria [8]. Considering that hypertension is associated with the severity of proteinuria in both diabetic and non-diabetic individuals, reducing proteinuria using ACE-I/ARB is a straight forward to decrease the risk of rapid decline in renal function in patients with proteinuria. The results of some current studies have suggested that the discontinuation of ACE-I/ARB in patients with advanced CKD might increase eGFR or delay its decline. However, a latest clinical study showed that

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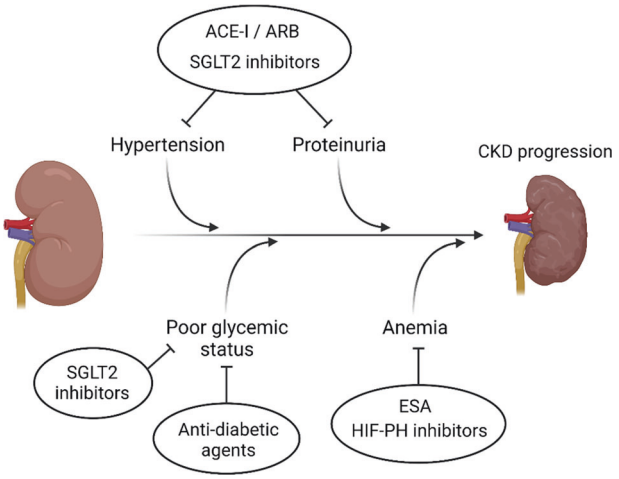

Fig. 1 Clinical parameters regulating the progression of CKD. Hypertension, severe proteinuria, poor glycemic status, and severe anemia are associated with progression of CKD. ACE-I angiotensin convertingenzyme inhibitors, ARB angiotensin II type 1 receptor blocker, ESA erythropoietin stimulating agents, HIF-PH hypoxia-inducible factor prolyl hydroxylase

discontinuation of ACE-I/ARB did not affect the prevalence of end stage kidney disease or initiation of renal replacement therapy in patients with CKD stage 4–5 [10]. Considering the result of another study showing that discontinuation of ACE-I/ARB is linked to high prevalence of cardiovascular events without affecting renal outcome [11], it would be better to use even a small amount of ACE-I/ARB in elderly with advanced CKD.

In the current study, the proportion of patients with 2 + to 3 + of proteinuria in diabetic population is about 5.7 times higher than that in non-diabetic population, 4.09% versus 0.72%, respectively [8]. In addition, poor glycemic control is linked to high risk of rapid decline in renal function in diabetic population, suggesting that the patients with diabetes are more likely to develop rapid decline in renal function with an increase in proteinuria. To prevent diabetes-related complications, a novel class of oral agents have been developed and launched in the clinical practice. In particular, sodium-glucose cotransporter 2 inhibitors (SGLT2i) have drawn the attention due to its striking renoprotective effect. SGLT2i are shown not only to lower HbA1c level by 0.6–0.8 % and improve lipid profile, but also to reduce intraglomerular pressure via tubuloglomerular feedback with a reduction in sBP by 4.43 mmHg [12]. Thus, several clinical studies have demonstrated that SGLT2i, in addition to ACE-I/ARB, are expected to preserve renal function during long-term period in patients with diabetes [13] as well as patients without diabetes [14]. Mechanistically, SGLT2i are reported to protect proximal tubules via attenuating mitochondrial dysfunction, reducing oxidative stress, affecting metabolic profile, and suppressing proximal tubule-regulated reabsorption of albumin. Thus, SGLT2i are one of the suitable partners of ACE-I/ARB to protect kidneys under both hyperglycemic and normoglycemic conditions (Fig. 1).

So far, low level of hemoglobin is shown to be associated with an increased risk of all-cause mortality, cerebrovascular events, and myocardial infarction [15]. However, whether anemia worsens CKD is still under debate. Fujii et al. demonstrated that relative risk of rapid decline in renal function was elevated with a decreased hemoglobin level in patients with and without diabetes [8]. The finding may provide the new insight regarding the relationship between anemia and CKD progression. Further clinical studies will be required to investigate the longitudinal impact of anemia and therapeutic options such as erythropoiesis stimulating agents or hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors for renal anemia on the progression of CKD in Japanese population. Taken together, the findings by Fujii et al. provide new insights regarding therapeutic clinical goals to discuss what we should aim for to delay CKD in the Japanese population.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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