Hypertension Research (2023) 46:339–340
https://doi.org/10.1038/s41440-022-01114-9

COMMENT

The public health impact of hypertension and diabetes: a powerful tag team for the development of chronic kidney disease

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Keywords Hypertension · Diabetes mellitus · Chronic kidney disease · Population attributable fraction

Received: 3 October 2022 / Accepted: 21 October 2022 / Published online: 6 December 2022

Diabetes mellitus (DM) is the leading cause of chronic kidney disease (CKD) in many areas of the world [1]. In contrast, hypertension (HT) is the most common cause of CKD burden in some areas, including east Asia [1], although those with HT are at relatively low risk of developing CKD [2]. The global prevalence of HT is substantially higher than that of DM; [1] thus, the population impact of HT on CKD is high. In addition to considering the relative risk of each risk factor for developing CKD, it is critically important to consider the population attributable fraction (PAF) of each risk factor for a public health approach.

In this issue of *Hypertension Research* [3], Kaneyama et al. conducted a longitudinal study of Japanese health screening data and showed that the risk of developing CKD, defined as reduced eGFR or proteinuria, was substantially higher and accompanied by a higher PAF in patients who had both HT and DM compared to those who had DM alone. Of note, the combination of HT and DM, compared to HT alone, had a greater impact only on the development of proteinuria and not on reduced renal function. These findings suggest that the risk of developing proteinuria among patients with HT is augmented by the concomitant presence of DM and/or vice versa. Interestingly, the significant effect on the development of reduced eGFR was only seen in patients with HT alone.

Patients with hypertensive nephrosclerosis are known to have an inherently low risk of developing blood pressure (BP)-dependent kidney damage [2]. However, a large number of patients develop CKD due to HT worldwide [1]. Various comorbidities may increase the risk of developing CKD [2]. Obesity has been suggested to play an important role as a risk factor since the global prevalence of obesity is increasing [1]. Kohagura et al. reported that obesity is associated with a BP-dependent increase in proteinuria in patients with nephrosclerosis [4]. Kaneyama et al. reported that patients with HT alone whose body mass index (BMI) was higher than that of a control group were significantly associated with new-onset proteinuria as well as reduced eGFR, with the highest PAF. Patients with DM are prone to glomerular hyperfiltration via various mechanisms, including hyperinsulinemia itself. Patients with a combination of HT and DM had the highest BMI among the groups and showed the highest risk of developing proteinuria but not reduced eGFR during a mean three-year follow-up study [3]. A previous larger-scale study conducted among Chinese patients reported that individuals with baseline HT and incidental DM, who were characterized by a higher BMI than those without incidental DM, showed a significantly higher risk of reduced eGFR during a median seven-year follow-up [5]. These findings suggest that comorbidities that disrupt the autoregulatory mechanisms of afferent arterioles, such as DM, may augment the risk of progression of proteinuria but initially mask the potentially reduced eGFR in hypertensive patients. A previous animal study also suggested a synergistic effect of increased BP and hyperglycemia causing kidney injury via glomerular hyperfiltration [6]. Consistent with this hypothesis, an autopsy study showed that the combination of HT and DM is synergistically associated with larger glomerular volume, which morphologically suggests glomerular HT [7]. Importantly, HT alone and the combination of HT and DM have a substantially higher PAF [4]. Thus, we must recognize that an approach targeting HT is crucially important for public health.

Another previous study revealed that diabetic patients had a higher risk of proteinuria but a lower risk of reduced eGFR (<60 mL/min/1.73 m^2) in the Japanese general population [8]. However, the impact of DM without HT on the development

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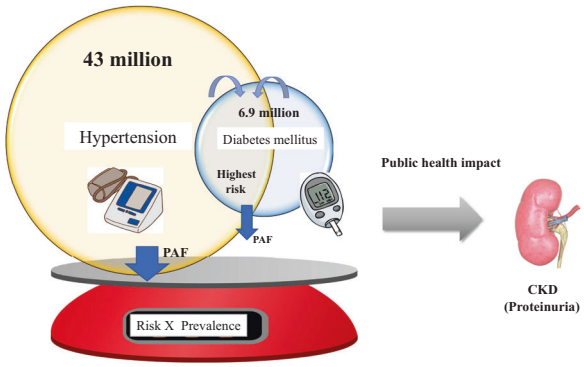

Fig. 1 Public health impact of concomitant hypertension and diabetes mellitus and that of hypertension alone on developing chronic kidney disease in Japan. CKD chronic kidney disease, PAF population attributable fraction

of CKD has not been fully elucidated. In Kaneyama's study, DM only was not associated with an increased risk of the development of proteinuria or reduced eGFR. As the authors discuss, many of the patients with DM in the study may not have had a long history of DM, leading to inadequate power detection. Additionally, patients with DM do not always have a comparable risk of developing CKD. Among diabetic patients, the subgroup characterized by extreme insulin resistance showed the highest risk of the development of albuminuria and renal decline. Hyperinsulinemia stimulates sodium reabsorption in each segment of the tubules, which is linked to salt-sensitive hypertension and disrupts autoregulation of the afferent arteriole. The aforementioned larger-scale Chinese longitudinal study showed that patients with DM and newly developing HT had a significantly higher risk of reduced eGFR than those with DM but no developing HT [5]. Kanayama et al.'s study showed that the coexistence of HT may exert a substantial impact on the development of proteinuria among patients with DM. This finding suggests that the approach for the prevention and management of HT is pivotal for preventing the development of CKD among patients with DM. Consistently, the Japan Diabetes Optimal Integrated Treatment Study for 3 major risk factors for cardiovascular diseases (J-DOIT3) study, which demonstrated the effectiveness of a multifaceted approach to risk factors in patients with DM, reported that BP control at 1 year contributed significantly to the prevention of renal damage in patients with reduced eGFR (<60 mL/min/1.73 m^2) [9]. Although stricter BP control is recommended for patients with DM, the rate of achievement of target BP levels is low in patients with DM [10].

In conclusion, with the given caveats, this study by Kaneyama et al. reminds us of the public health impact of HT on developing CKD, especially the synergistic interaction with DM (Fig. 1). We need to challenge "inertia" to achieve target BP control, especially among patients with concomitant DM and HT.

Compliance with ethical standards

Conflict of interest KK received personal fees for lectures from AstraZeneca, Daiichi Sankyo, Mitsubishi Tanabe Pharma, and Boehringer Ingelheim.

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