Review Article

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Blood Pressure Control in Patients with Diabetic Kidney Disease

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Diabetic kidney disease (DKD) is the most common cause of end-stage kidney disease. Blood pressure (BP) control can reduce the risks of cardiovascular (CV) morbidity, mortality, and kidney disease progression. Recently, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines have suggested the implementation of a more intensive BP control with a target systolic BP (SBP) of <120 mmHg based on the evidence that the CV benefits obtained is outweighed by the kidney injury risk associated with a lower BP target. However, an extremely low BP level may paradoxically aggravate renal function and CV outcomes. Herein, we aimed to review the existing literature regarding optimal BP control using medications for DKD.

Key Words: Blood pressure, Diabetes, Kidney, Mortality

INTRODUCTION

Diabetic kidney disease (DKD) is the most common cause of end-stage kidney disease (ESKD) worldwide[1]. According to the Korean ESKD registry (Korean Renal Data System, KORDS), its incidence has exponentially increased from 10% in 1985 to 49.8% in 2020[2]. The initial clinical manifestations of DKD include glomerular hyperfiltration, albuminuria, and arterial hypertension, which eventually lead to a lower estimated glomerular filtration rate (eGFR)[3]. The progression of chronic kidney disease (CKD) is considerably faster in patients with diabetes than that in patients without diabetes[4].

The renin-angiotensin-aldosterone system (RAAS) is the most important treatment target. RAAS activation increases the glomerular capillary hydraulic pressure and disrupts the renal vascular autoregulation, causing further renal damage[5]. Hence, rigorous control of RAAS activation is crucial for blood pressure (BP) and urinary albumin level control in DKD management.

Recent clinical studies have shown that strict BP control can reduce cardiovascular (CV) morbidity and mortality rates, as well as the progression of kidney diseases. However,

a considerable decrease in BP levels may paradoxically aggravate the renal damage[6,7]. Accordingly, when determining the optimal BP control for the prevention of CV events and all-cause death, the renal function status and risk of ESKD should be taken into consideration. Currently, the target BP for patients with diabetes is frequently used, as no randomized controlled trials (RCTs) have determined the target BP for patients with DKD.

A multidisciplinary approach is recommended to delay the deterioration of renal function in patients with DKD. Although this study examined the antihypertensive medications used in patients with DKD, lifestyle modifications, including a low-salt diet, exercise, smoking cessation, and weight control, require prioritization. In addition, recent clinical trials on the use of sodium-glucose cotransporter 2 inhibitors, finerenone, and selective endothelin A receptor antagonists have shown promising results. Sodium-glucose cotransporter 2 inhibitors and finerenone have been recommended in the latest Kidney Disease Improving Global Outcomes (KDIGO) guidelines[8]. Although these agents are beyond the scope of this review, their use may attenuate the progression of renal disease in patients with type 2 diabetes. Hence, we aimed to review the existing literature on optimal BP control using medications in these patients.

Renal hemodynamics in diabetic kidney disease: The relationship between albuminuria, hypertension, and renal function

In patients with type 1 diabetes, hypertension develops concurrently with albuminuria or overt nephropathy; in patients with type 2 diabetes, hypertension often precedes albuminuria, and the eGFR declines[4,9]. Hypertension coexists with other CV risk factors, such as insulin resistance, dyslipidemia, and obesity. These risk factors can further exacerbate systemic hypertension and may be a cause as well as a consequence of the deterioration of renal function. Systemic hypertension increases intraglomerular pressure, inducing hyperfiltration and proteinuria[5]. Furthermore, the overproduction of vasoactive factors disrupting renal vascular autoregulation worsens glomerular hyperfiltration, in which RAAS activation plays a crucial role[10,11]. The local production of angiotensin II induces intraglomerular hypertension, proteinuria, and inflammatory pathways, which contribute to the development of the pathognomonic features of DKD, such as glomerular hypertrophy and sclerosis, tubulointerstitial inflammation, and fibrosis[12].

An increase in urinary albumin excretion (UAE) is an early renal manifestation of generalized vascular dysfunction and may serve as an indicator of renal and CV risks[13]. The UAE rate, even within the normal range, is associated with changes in BP levels, development of hypertension, and renal vascular resistance, which are particularly evident in the presence of renal dysfunction[14,15]. An increase in albuminuria is a predictor of ESKD progression[15]. Recent studies have confirmed that an increase in the UAE rate leads to poor CV and renal outcomes, while reduction of albuminuria attained through optimal BP control is associated with a favorable prognosis[16,17]. Therefore, the reduction of albuminuria may serve as a treatment target because alterations in urinary albumin levels may reflect parallel changes in both CV and renal risks[18].

Patients with diabetes and normoalbuminuria may present with different clinical manifestations. CKD may present heterogeneously in patients with type 1 and type 2 diabetes, with differing histological patterns and variations in the extent of fibrosis and ischemia involving the tubules, glomeruli, and interstitium[19]. Albuminuria may be absent or minimal in a significant proportion of patients with diabetes with declining renal function[20]. Higher BP levels deteriorate renal function regardless of the albuminuria status[21]. For instance, the United Kingdom Prospective Diabetes Study (UKPDS) showed that each 10 mmHg increase in mean BP caused a 15% increase in the hazard ratios for CKD development or a twofold increase in the serum creatinine levels in patients with normoalbuminuria[22]. Although the renal outcomes in patients with diabetes with traditional "albuminuric" phenotype have improved by maximal RAAS inhibition and BP lowering, the utility of corresponding treatments when albuminuria is not present remains unclear. For patients with non-classic phenotypes of DKD presenting with minimal albuminuria, the appropriate antihypertensive treatment and antihypertensive drug combinations should be determined based on the target BP values[18].

Albuminuria is generally recognized as an indicator of and a treatment target for slowing the progression of kidney disease, and renoprotection is achieved by the reduc-

tion of albuminuria[23]. The United States Food and Drug Administration recently accredited the changes in albuminuria as the target marker for kidney disease progression in various clinical trials[24]. In addition, persistent hypertension may cause albuminuria, which may precede and even predict the development of hypertension, particularly in patients with low eGFR[14]. Considering the bidirectional relationship between hypertension and albuminuria, the optimal BP may require the reduction of albuminuria and tolerable decline in eGFR in patients with DKD.

Adequate measurement of blood pressure: Standardized versus routine office blood pressure measurement

In the 2021 KDIGO BP guidelines, the standardized office BP measurement was recommended over routine office measurement[8]. This recommendation was also previously incorporated in the 2017 American College of Cardiology/American Heart Association guidelines[25]. As BP levels based on office measurements tend to be higher than standardized BP measurements[26], overtreatment and hypotensive events may be possible.

Several considerations should be taken into account when performing the standardized office BP measurements, that is, from the preparation to the actual measurement[8]. For instance, the patients are required to empty their bladders and refrain from consuming caffeine, exercising, and smoking for at least 30 min before the BP measurement. Additionally, patients should attempt to relax for more than 5 minutes while seated in a chair with back support and place both feet on the ground. Neither the patient nor the observer may talk during the 5-minute rest period and throughout the procedure. The cuff is placed directly on the skin, away from the patient's clothing. During the measurement, adequate arm support is provided, and an adequately sized cuff, with a bladder length that covered 80% of the patient's arm circumference should be placed on the upper arm of the patient. BP measurements are taken once in both arms, and subsequent measurements are taken in the arm with a higher BP level. A minimum of two BP measurements at 1- to 2-minute intervals were required, and the average of the measurements are recorded. Both systolic BP (SBP) and diastolic BP levels are recorded along with the antihypertension medication that the patient recently took before the BP measurement.

Notably, the American Diabetes Association (ADA) consensus panel has indicated that a 24-h ambulatory BP measurement is relevant in identifying the at-risk subgroups of patients with diabetes[27]. This may be due to the fact that masked hypertension and nocturnal non-dipping BP status are possible confounding variables in the relationship between office BP measurement and DKD progression[28]. Furthermore, standing or seated BP should be used as a target for treatment as some patients with diabetes and hypertension may develop autonomic neuropathy manifested as orthostatic hypotension and impaired systemic hemodynamics[29].

Target blood pressure for patients with diabetic kidney disease

For the past two decades, the target BP levels in patients with and without albuminuria have been <130/80 mmHg and <140/90 mmHg, respectively[30]. Recent results from the Systolic Blood Pressure Intervention Trial (SPRINT) challenge this traditional school of thought[7]. This study demonstrated favorable results of intensive BP control, with a target SBP of <120 mmHg (mean BP, 121.4 mmHg), compared with that of the conventional target of <140 mmHg (mean BP, 136.2 mmHg). Adopting the results from the SPRINT, the KDIGO 2021 guidelines updated their recommendation to a target SBP of <120 mmHg in patients with CKD[8]. However, given the negative results of intensive BP control from several key studies[6,31,32], other guidelines do not subscribe to the use of strict target BP levels and still recommend different targets for patients with CKD (Table 1)[6,31,32].

Nevertheless, mounting evidence appears to support the efficacy of intensive BP control in reducing adverse CV events and all-cause mortality rates, in patients with CKD with and without diabetes. In previous studies, a BP target of >140 mmHg in patients with CKD with diabetes was regarded as suboptimal[33-36]. The UKPDS also noted favorable outcomes with tighter BP control (mean BP, 144/82 mmHg vs. mean BP, 154/87 mmHg) in terms of diabetes-related outcomes, mortality, stroke, and microvascular complications[33]. Additionally, two studies that conducted posthoc

Table 1. Guideline comparisons of goal BP for diabetic patients with hypertension

Guideline	Target population	Target BP
2022 ADA	Diabetes	<140/90
	Diabetes with higher CV risk	<130/80
2021 KDIGO	CKD with or without proteinuria	SBP <120*
2020 ISH	CKD with or without proteinuria	<130/80
2018 ESC/ESH	CKD with or without proteinuria	SBP 130-139
ACC/AHA 2017	Diabetes	<130/80
	CKD 3 or beyond	<130/80
KDA 2021	Diabetes	<140/85
	Diabetes with CVD	<130/80
KSH 2022	Diabetes with low risk**	<140/90
	Diabetes with high risk**	<130/80

BP, blood pressure; ADA, American Diabetes Association; CV, cardiovascular; KDIGO, Kidney Disease: Improving Global Outcomes; CKD, chronic kidney disease; ISH, International Society for Hypertension; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ACC, American College of Cardiology; AHA, American Heart Association; KDA, Korean Diabetes Association; KSH, Korean Society of Hypertension.
*Using standardized office BP measurement
**Asymptomatic organ damage or one or more risk factors for cardiovascular disease

analyses, the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study and the Irbesartan Diabetic Nephropathy Trial (IDNT), showed an association between lower BP levels and improved renal outcomes[37,38]. In a meta-analysis of 123 trials that included 613,815 participants, the risks of major CV events and all-cause mortality were notably lower with every 10 mmHg reduction in SBP[39]. A pooled analysis of four multicenter RCTs including 4,983 patients with CKD also reported that an SBP target of <130 mmHg was associated with decreased all-cause mortality and CV outcomes compared with the standard BP target of <140 mmHg, excluding patients with an eGFR of $\geq$60 mL/min/1.73 m^2 and who had undergone intensive glycemic control[40].

Several studies have demonstrated the efficacy of intensive BP control. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial involving 11,140 patients with type 2 diabetes confirmed that the risk of significant renal events was reduced with a lower BP level (mean SBP, 134.7 vs. 140.3 mmHg), which was driven by the reduced risks of developing both micro- and macroalbuminuria[41]. In this study, progressively lower numbers of renal events were observed in patients with increasingly lower SBP levels (<110 mmHg). In the SPRINT, which is the most important clinical study investigating the effectiveness of intensive BP control, intensive BP control had beneficial effects on patients with a risk of experiencing serious adverse effects, such as hypotension, syncope, electrolyte abnormalities, and kidney injury.

However, results on the evaluation of the efficacy and safety of intensive SBP reduction to <120 mmHg were contradicting. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials involving patients with type 2 diabetes, strict SBP control to <120 mmHg (mean BP, 119.3 mmHg) had no association with CV and renal protection compared with the standard SBP target of <140 mmHg (mean BP, 133.5 mmHg), except for the risk of stroke[6]. Furthermore, interventions that substantially lowered the SBP level to <120 mmHg were associated with an increased risk of adverse kidney events, such as higher serum creatinine levels or an eGFR of <30 mL/min/1.73 m^2 [6]. The corresponding SBP intervention in the SPRINT also demonstrated a higher incidence of adverse renal outcomes in those without diabetes[7]. Beddhu et al. compared the intensive and standard SBP groups in both SPRINT and ACCORD trial[42]; the intensive intervention group showed an increased risk of incident CKD regardless of the status of type 2 diabetes. Interestingly, the absolute risk was higher in patients with diabetes than in those without diabetes.

The Appropriate Blood Control in Diabetes study also examined the effect of maintaining a lower BP target of <130/80 mmHg (mean, 128 mmHg) for 5 years on the preservation of renal function compared with that of achieving the standard target of <140/90 mmHg (mean: 137 mmHg) in patients who are normotensive with type 2 diabetes; however, no evidence was found to support the efficacy of intensive BP control[43].

In addition to safety issues, some studies have shown a U-shaped association between SBP and the risk of mortality. An observational subgroup analysis in the International Verapamil SR-Trandolapril study showed that an SBP level of <110 mmHg showed a significantly increased risk of all-cause mortality compared with SBP levels of 125-130 mmHg[44]. Several cohort studies have also suggested the risks associated with a considerable BP reduction[45-47]. In a previous meta-analysis, BP-lowering treatments reduced the incidence of CV events, particularly in high-risk patients with various comorbidities, but they had no proportional effects in patients with a lower baseline SBP of <130 mmHg [39]. According to these results, the international guidelines that defined the optimal BP values have recently been revised, with recommendations including an SBP target of <130 mmHg for high-risk patients, such as those with diabetes or CKD[25,48-50].

A few limitations exist in the current RCTs. These involve diverse groups of patients but largely exclude patients with CKD or those with diabetes and advanced CKD. Notably, the SPRINT reported a mean eGFR of 48 mL/min/1.73 m^2, mostly involving patients with CKD stage G3a; however, the study only included those in the prediabetes stage, which was present in 36.5% of the patients[7]. Another important study, the ACCORD trial, excluded patients with a serum creatinine level of >1.5 mg/dL. Meanwhile, the BP measurements in the SPRINT were performed under ideal conditions; that is, the patients were resting in a quiet room for 5 minutes without an observer, which may have induced a reduction in BP levels compared with that performed in other clinical trials. However, these conditions may not be applicable in a real clinical setting. The KDIGO guidelines suggest that an SBP target of <120 mmHg obtained using non-standardized BP measurement methods may be potentially harmful. Therefore, caution should be taken when applying the updated guidelines of intensive BP control in patients with DKD.

Blood pressure lowering on albuminuria

The optimal goal for BP control in patients with CKD includes the prevention of CV events and all-cause death as well as the prevention of incident CKD and attenuation of CKD progression. Although intensive BP control fails to preserve the GFR, it has been shown to reduce the risk of albuminuria. The ACCORD trial found that intensive BP control considerably reduced the risk of macroalbuminuria, even though a higher risk of CKD was noted. In the ADVANCE trial, a reduction in the risk of microalbuminuria and macroalbuminuria was achieved through active BP control[41,51]. Furthermore, when albuminuria was reduced, independent of the BP status or antihypertensive regimen used, the increased risks of CV and renal outcomes were attenuated in patients with CKD who did not have diabetes[16,52].

However, the results of these studies, particularly the short-term data, should be interpreted with caution because albuminuria reduction may also result from GFR reduction[53]. These studies showed that lowering the BP levels may result in the simultaneous reduction of albuminuria and eGFR. Nevertheless, considering that various markers of kidney injury did not significantly increase despite the increase in serum creatinine levels, decreased eGFR may only reflect alterations in hemodynamics achieved by intensive BP control[54,55]. Therefore, a reasonable decrease in the eGFR followed by a gradual recovery may be acceptable, as their effects on the CV outcomes of albuminuria reduction related to BP lowering are favorable.

Strategies to control blood pressure in patients with diabetic kidney disease

Results from patients with and without diabetes have shown that RAAS blockade provides a renoprotective effect, along with a reduction in proteinuria and attenuation of eGFR decline. In the African American Study of Kidney Disease and Hypertension trial, the angiotensin-converting enzyme inhibitor (ACEi)-treated group showed a slower eGFR decline than those who received other treatments[56]. In the RENAAL and IDNT studies involving patients with type 2

diabetes and CKD, the use of angiotensin II receptor blockers (ARBs) attenuated the progression of CKD[57,58]. However, combination therapy with ACEis and ARBs is not recommended as it causes a greater decline in renal function and hyperkalemia[59-61]. Hyperkalemia related to RAAS blockade frequently occurs in patients with diabetes and a novel potassium binder patiromer can be used in those with CKD stages 3 to 4, and on RAAS blockade (ACEi/ARB, spironolactone)[62]. For patients with albuminuria or CV diseases, ACEis and ARBs are the first-line antihypertensive medications.

However, the efficacy of ACEi and ARB as first-line therapy in the absence of albuminuria remains unclear. In the Bergamo Nephrologic Diabetes Complications Trial, ACEi prevented the onset of microalbuminuria in patients with type 2 diabetes but with normal urinary albumin excretion, representing those with early-stage CKD without microalbuminuria[63]. The Randomized Olmesartan and Diabetes Microalbuminuria Prevention study also showed delayed onset of microalbuminuria in similar conditions[64]; however, significant fatal CV events occurred in the treatment group. Bangalo et al. also reported that no evidence was found regarding the superiority of RAAS blockade over other BP medications[65]. In the absence of albuminuria, maintaining a BP level of <130 mmHg but above 120 mmHg may be prudent[66]. Lower BP targets may be appropriate when the potential for kidney injury with intensive BP control is minimal and reversible, and the benefits against adverse CV events outweigh those of renal events.

With accumulating evidence of various pleiotropic effects conferred with respect to cardio and renoprotection, SGLT2i and GLP1RA have emerged as a game changer in the management strategy for DKD. Study results of various clinical trials were accepted by renowned societies including the ADA, the European Association for the Study of Diabetes and the KDIGO, recommending SGLT2i and GLP1RA as first-line therapies for patients with DKD[67,68]. The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial demonstrated that risk of kidney failure or death from CV or renal causes was reduced with dapagliflozin and was even effective in patients with CKD without diabetes[69]. Apart from their significant impact on lowering adverse CV events and death[70-72], BP can be reduced by 5 mmHg by these drugs[73,74].

A highly selective endothelin A receptor (ETAR) antagonist, atrasentan can reduce albuminuria even with its short-term use in patients with DKD[75]. The long-term use of atrasentan was evaluated in 2,648 patients with type 2 diabetes and overt albuminuria in the Study of Diabetic Nephropathy with Atrasentan[76]. Composite adverse kidney outcome of doubling serum creatinine or kidney failure with replacement therapy was greatly reduced from atrasentan therapy. Its potential in proteinuria reduction should also be acknowledged with evidence from outcome of those with primary focal segmental glomerulosclerosis when used in combination with a dual ETAR antagonist (sparsentan) and ARB in a recent Phase 2 study[77]. It is also reported that BP is significantly lowered by ETAR antagonists[77,78].

Lastly, mineralocorticoid receptor antagonists (MRAs) provide cardioprotection and renoprotection[79,80]. A first-generation nonselective MRA, spironolactone, was first known to provide renoprotection in non-diabetic patients with CKD by proteinuria reduction and eGFR preservation[81]. Then, finerenone, a next-generation selective MRA, proved to be a potential measure for DKD management showing its effective risk reduction in terms of CKD progression and CV events development in patients with CKD and diabetes in the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease study[82]. People with resistant hypertension can even lower their BP with MRAs as well[83,84].

A recent retrospective study acknowledged the importance of consistent BP control[53]. Only 28% of patients achieved the target BP, with those remaining showing an increased risk of DKD (odds ratio 1.38) and albuminuria (odds ratio 1.47) within a period of 4 years. Therefore, adherence to the medication regimen is essential. Currently, several guidelines emphasize the non- or suboptimal adherence to antihypertensive medications as a hindrance to achieving consistent BP target.

CONCLUSIONS

The optimal BP control goal in patients with DKD should include the attenuation of renal functional deterioration and improvement of CV outcomes. Despite substantial at-

tempts to address these factors, the optimal BP level in patients with DKD remains unknown. The recently updated KDIGO 2021 guidelines recommend the implementation of intensive BP control, with a target SBP level of <120 mmHg, based on the evidence that the CV benefits obtained is outweighed by the kidney injury risk associated with a lower BP target. However, different BP targets may be necessary, based on age, type of diabetes, and CKD stages. Lesser aggressive treatment strategies may be used in older and frail patients with non-albuminuric renal impairment, based on the paradoxical J-curve relationship between BP reduction and renal and CV morbidity[85]. However, future trials are needed to clarify other uncertainties. Well-designed RCTs may be able to evaluate the effects of intensive BP control through the use of various interventions in diverse patient populations, including patients with CKD with and without diabetes, those with a high CV risk or proteinuria, and those with early- and late-stage CKD. These trials may ultimately better determine the cutoff BP target values in these patients.

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