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REVIEW ARTICLE

Blood pressure management and renal protection: Revisiting hypertensive nephropathy

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Abstract: Hypertension has traditionally been the most common cardiovascular disease, and epidemiological studies suggest that the incidence continues to rise. Despite a plethora of antihypertensive agents, the management of blood pressure (BP) remains suboptimal. Addressing this issue is paramount to minimize hypertensive complications, including hypertensive nephropathy, a clinical entity whose definition has been challenged recently. Still, accumulating studies endorse poorly managed BP as an independent risk factor for both the onset of renal dysfunction and aggravation of baseline kidney disease. Nevertheless, current recommendations are not only discordant from one another but also offer inadequate evidence for the optimal BP control targets for renal protection, as since the cutoff values were primarily established on the premise of minimizing cardiovascular sequelae rather than kidney dysfunction. Although intense BP management was traditionally considered to compromise perfusion toward renal parenchyma, literature has gradually established that renal prognosis is more favorable as compared with the standard threshold. This review aims to elucidate the renal impact of poorly controlled hypertension, elaborate on contemporary clinical references for BP control, and propose future directions to improve the holistic care of hypertensive individuals.

Keywords: Antihypertensive agents; Blood pressure; Hypertensive nephropathy

1. INTRODUCTION

With the evolution of contemporary lifestyle and diet habit, cardiovascular disease, following cancer, stands as the second leading cause of death globally.[1] Of which, hypertension is one of the most frequently encountered clinical issues, though with inadequate attention. According to global epidemiological documentations, around 31.1% of individuals worldwide have hypertension and the prevalence is constantly rising.[2] Although plenty of traditional risk factors contributing to hypertension have been identified and despite the introduction of abundant antihypertensive medications in the past decades, management of blood pressure (BP) in the modern society is still suboptimal, as one-fourth of the hypertension sustainers fail to reach optimal BP targets. Moreover, poorly controlled BP was reported to predispose these patients to end organ complications. Lewington et al[3] suggested once BP exceeds 110/75 mmHg, every 20/10 mmHg BP increase doubles the risk of cardiovascular sequelae. Secondary analysis of the Systolic Blood Pressure Intervention (SPRINT) trial further suggested optimal BP control offered a survival benefit up to 3 years in patients without diabetes mellitus (DM).[4] Regulation of BP level therefore harbors important clinical significance.

Despite the understanding of hypertension and cardiovascular burden, the relationship between elevated BP and renal dysfunction awaits further investigations. Patients with hypertension often endorsed other cardiovascular, renal, and metabolic complications. Statistics suggest that 84% of adults with chronic kidney disease (CKD) and half of patients with DM sustained hypertension, and this association was independent of ethnicity.[5,6] DM leads to hypertension due to plethoric body fluid and vascular remodeling. DM is one of the causes of elevated renal sodium reabsorption and induced peripheral vasoconstriction in CKD. Hypertension is an inevitable consequence of renin-angiotensin-aldosterone system (RAAS) activation in conjunction with antagonism of nitrite oxide and excitation of endothelin 1 to impact hemodynamics. Management of BP therefore mandates the consideration and treatment of these comorbidities. For example, progression of albuminuria is known to indicate renal function deterioration. Systematic high BP results in elevated glomerular burden and excess protein loss, which eventually leads to overt proteinuria. Cumulative evidence also attributes increased renal and cardiovascular mortality rate to proteinuria. In the Ramipril Efficacy in Nephropathy study, an angiotensin-converting enzyme (ACE) inhibitor, ramipril, was demonstrated to curb proteinuria and improve renal prognosis in the nondiabetic population.[7] However, the renal benefit exerted by strict BP control in patients with CKD has not been demonstrated by landmark trials (Table 1). In addition, current guidelines recommended target BP for the primary purpose of preventing adverse cardiac events, whereas functional impairment of other target organs, for example, kidneys, is seldom addressed.

In this review, we clarify the pathophysiology of hypertensive nephropathy, critically appraise current evidence on BP control to

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Table 1

Renal efficacy by BP lowering in patients with CKD

Trial, year	BP target (mmHg)	Subjects with CKD (%)	Renal benefit
MDRD, 1994[35]	SBP 125 vs 140	100	Negative if proteinuria <1 g; positive otherwise
AASK, 2002[37]	SBP 128 vs 141	100	Negative
REIN-2, 2005[c]	SBP 130/80 vs DBP 90	100	Negative
ADVANCE, 2007[d]	SBP 135 vs 140	19	Negative
ACCORD, 2010[e]	SBP 120 vs 140	9	Negative
SPS3, 2013[f]	SBP 130 vs 140	16	Negative
SPRINT, 2015[g]	SBP 120 vs 140	28	Negative
HOPE-3, 2016[h]	SBP 128 vs 134	3	Negative

Historic landmark trials to evaluate if BP management limits the aggravation of renal insufficiency.
AASK = African American Study of Kidney Disease and Hypertension; ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation; BP = blood pressure; CKD = chronic kidney disease; DBP = diastolic blood pressure; HOPE = Heart Outcomes Prevention Evaluation; MDRD = Modification of Diet in Renal Disease; REIN = Ramipril Efficacy in Nephropathy; SBP = systolic blood pressure; SPRINT = Systolic Blood Pressure Intervention; SPS3 = Secondary Prevention of Small Subcortical Strokes Trial.
[c]*Lancet* 2005;365:939–46.
[d]*Lancet* 2007;370:829–40.
[e]*N Engl J Med* 2010;362:1575–85.
[f]*Lancet* 2013;382:507–15.
[g]*N Engl J Med* 2015;373:2103–16.
[h]*N Engl J Med* 2016;374:2021–31.

Table 2

Studies on the association between BP and renal function

Author (year)	Cohort details	Finding
For correlation		
Mitsnefes et al (2003)[10]	3834 patients aged 2-17 years old, eGFR ≤75 mL/min/1.73 m2	Hypertension is an independent risk factor of renal disease progression in pediatric population.
Walker et al (1992)[15]	5524 hypertensive males	BP control curbed renal impairment in non-Blacks.
Haroun et al (2003)[16]	23 534 Caucasians	Poorly controlled BP is a risk factor for CKD.
Tsai et al (2017)[24]	8127 patients (9 trials)	Intensive BP control benefited non-Black population on kidney disease progression.
Against correlation		
Lipkowitz et al (2013)[12]	1293 African Americans	Kidney injury remained prevalent albeit rigorous BP control.
Hsu (2001)[17]	26 521 subjects with baseline intact kidney function	Hypertension control does not reduce the rate of kidney dysfunction.
Xie et al (2016)[23]	44 989 participants (19 trials)	Stringent BP control failed to abate progression of renal dysfunction.

The historical studies supporting and opposing the relationship between hypertension and nephropathy are listed.
BP = blood pressure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

avoid renal function decline or antagonize the aggravation of CKD, and propose new directions for future guidelines on hypertension.

2. HYPERTENSIVE NEPHROPATHY

Previous observational studies have demonstrated that hypertension and nephropathy are closely intertwined. With hypertension being the second leading cause of end-stage renal disease (ESRD) following DM and the second most commonly diagnosed primary disease in patients with ESRD, epidemiological studies have documented more than 30,000 Americans with sustained hypertension-associated CKD.[8] In the Multiple Risk Factor Intervention Trial (MRFIT) with 332 544 males enrolled, hypertension was reported to associated with the development of subsequent ESRD, regardless of ethnicity.[9] As for the pediatric population, CKD leads to hypertension by activating the RAAS and increasing sympathetic tone, and further, poorly managed BP serves as a crucial factor in the aggravation of renal function decline and cardiovascular mortality, as noted in the North American Pediatric Renal Transplant Cooperative Study.[10] BP is also profoundly regulated by kidneys through RAAS.[11] The literature reaffirms the clinical existence of hypertensive nephropathy and the relationship between these two disease entities (Table 2).

However, whether or not hypertension itself can directly contribute to renal dysfunction has long been debated. The association between hypertension and nephropathy was first introduced two centuries ago and initially referred as nephrosclerosis. Lipkowitz et al[12] observed a high incidence of renal function impairment in the African American Study of Kidney Disease and Hypertension (AASK) cohort despite rigorous medical BP control. Genomes were then sequenced and therein identified that an apolipoprotein 1 (Apo 1) gene variant was closely intertwined with CKD progression, regardless of BP level. Apo 1 was later shown to cause both secondary hypertension and focal segmental glomerulosclerosis.[13] Therefore, mild-to-moderate BP elevation may be misattributed to nephropathy in this AASK population, and the identification of Apo 1 raised the opinion that hypertensive nephropathy may only represent an inadequate workup for renal disease.[14] On the contrary, further studies showed opposing findings in different ethnic background. In European Americans, likely due to fewer culprit genetic polymorphisms, renal function decline was successfully rescued by BP control in addition to the management of dyslipidemia and smoking abstinence.[15] Similarly, Haroun et al[16] conducted a subsequent 20-year prospective observational study including 23 534 Caucasian participants in Washington County, MD, and stated poorly controlled BP was a significant risk factor for CKD. To investigate whether nonmalignant hypertension brings about renal insufficiency, Hsu[17] meta-analyzed 10 randomized control trials and found that individuals who received antihypertensive medications did not exhibit a lower incidence of renal dysfunction. However, this analysis neglected the baseline renal status of participants and may misrepresent the association. Further, because renal biopsies are rarely performed in patients with both hypertension and nephropathy, the controversy remained unsettled.

3. PATHOPHYSIOLOGY

To better understand the correlation, further investigation on the pathophysiologic mechanism was attempted. In the early era, the development of hypertension and nephropathy was considered mutually causative. As a result, determining the respective roles in the pathogenesis was a challenge. Additionally, metabolic comorbidities, for example, hyperglycemia, hyperlipidemia, hyperuricemia, obesity, and atherosclerosis, further confounded the onset of kidney injury. Additionally, stringent BP control had not yet been correlated with renal protection. Some thus argued hypertension was actually heralded by renal dysregulation rather than being the cause of causing kidney injury.

However, the establishment of hypertensive nephropathy was solidified in the following decades based on the elucidation of underlying pathophysiologic machinery. The mechanism will be discussed in accordance to renal anatomy: arteriole and glomerulus, interstitium, and Bowman's capsule. First, elevated pulse pressure is known to stiffen the arteriole, which in turn elevates the sympathetic tone and activates RAAS.[18] Chronically, overloading

results in glomerular hypertrophy and eventually loss of renal autoregulation. The term "nephrosclerosis" was hence proposed to be replaced with "arterionephrosclerosis" to better emphasize such vasculopathy. Second, in the setting of angiotensin II–dependent hypertension, endothelin receptor and the transforming growth factor beta/Smad pathway are induced to trigger epithelial-to-mesenchymal transition and subsequent tubular-interstitial fibrosis,[19] possibly as a response to the state of inflammation and macrophages infiltration.[20] Third, an in vitro study that illustrated hypertension led to the activation of Ras-related C3 botulinum toxin substrate 1 in podocytes through four-and-a-half LIM domain protein 2 receptor and ultimately caused food process effacement.[21] These pathophysiological adaptations in response to hypertension together remodeled the renal manifestation (Fig. 1).

Taken together, the development of hypertensive nephropathy is multifaceted, as it is caused by the deteriorative effect of poorly managed BP via nephroangiosclerosis, glomerular hyalinosis, tubulointerstitial fibrosis, inflammation-induced epithelial-to-mesenchymal transition, and podocyte effacement. Therefore, instead of the traditional term "hypertensive nephropathy," "arterionephrosclerosis," or "atherosclerotic nephropathy" were proposed to better delineate the phenomenon and further emphasize the vascular consequences on renal system secondary to hypertension.

4. EFFECT OF INTENSIVE BP CONTROL ON RENAL FUNCTION

Following the establishment of hypertensive nephropathy, the next clinical question is to what extent BP should be maintained. Although the hypoperfusion of renal parenchyma secondary to rigorous BP control may induce more episodes of acute kidney injury,[22] the reduction of intraglomerular pressure better protects renal vasculature. Xie et al[23] meta-analyzed 44 989 individuals from 19 independent trials and concluded that intensive BP control curtailed the incidence of albuminuria but not ESRD. Tsai et al[24] noted that stringent BP control benefited non-Black individuals and subjects with baseline heavy proteinuria by abating the progression of renal dysfunction. Renal profiles, including doubling time of serum creatinine and estimated glomerular filtration rate (eGFR) changes, of patients with otherwise similar demographic and clinical backgrounds did not benefit from strict BP control.[24] As for patients naive to antihypertensive agents, whether or not serum creatinine would rise in the acute stage of drug administration depended on renal autoregulation ability.[25] Patients with CKD were predisposed to sustaining early renal dysfunction, which was associated with adverse outcomes.[26] However, when specifically considering the use of angiotensin II receptor blockers (ARB), acute renal function decline was reciprocally correlated with better renal prognosis due to its pharmacological mechanism of action.[27] These studies demonstrated the renal impact of effective BP control, though the exact threshold for BP target remained undetermined.

Still, guidelines recommendations on BP management not only vary based on the committee proposing them but also created with the goal to minimize cardiovascular adverse events instead of rather than other systematic impacts. Coinciding with the 2020 International Society of Hypertension guidelines which targeted BP at 140/90 mmHg for otherwise healthy subjects and 130/80 mmHg for patients with comorbidities,[28] European Society of Cardiology suggested a BP target range at 130/79 to 139/70 in patients with DM or CKD.[29] American College of Cardiology, on the other hand, set the target at 130/80 mmHg for patients with comorbidities.[30] Detailed comparisons between guidelines have been reviewed elsewhere.[31] The BP recommendations were also modified based on geographic characteristics and for pragmatic purpose. For example, Taiwan Society of Cardiology guideline was stricter for patients with hypertension-mediated organ damages or carry high cardiovascular risk.[32] Notably, the 2021 Kidney Disease: Improving Global Outcomes guidelines advised a target systolic BP <120 mmHg under standardized and proper measurements.[33] The optimal BP target for patient with intact renal

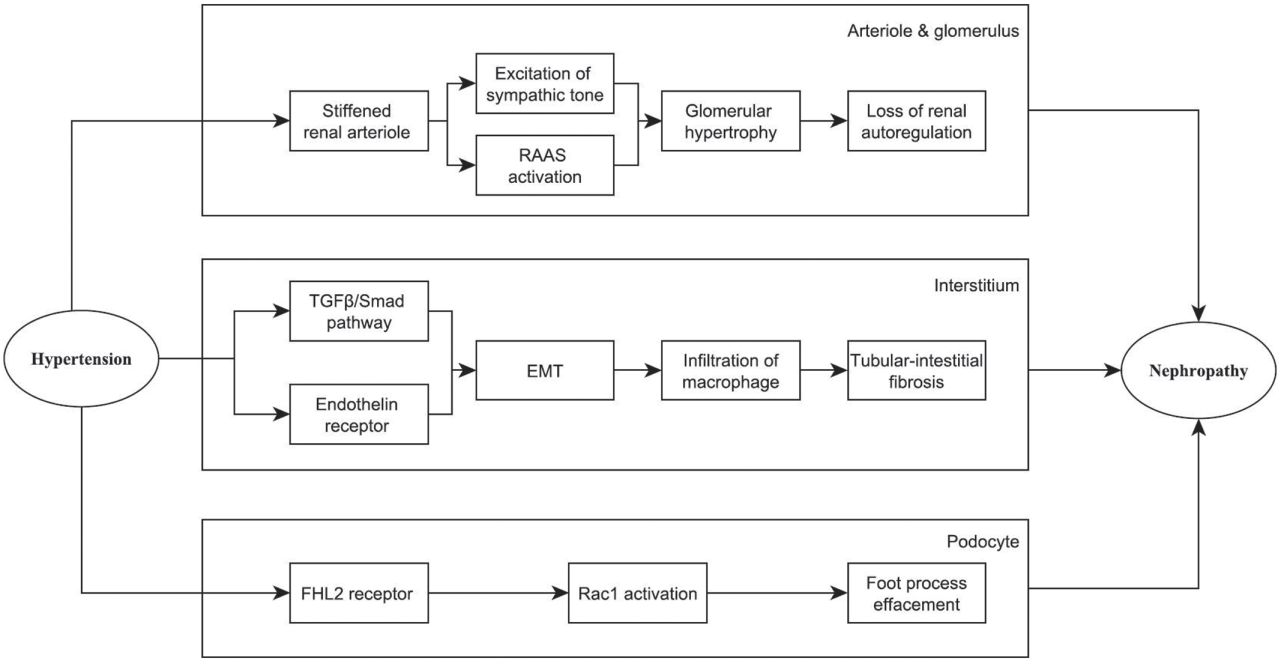

Fig. 1 Pathogenesis of nephropathy secondary to elevated BP. The mechanism of hypertensive nephropathy was summarized based on the renal anatomy, including arteriole and glomerulus, interstitium, and podocyte. EMT = epithelial–mesenchymal transition; FHL2 = four and a half LIM domains 2; RAAS = renin-angiotensin-aldosterone system; Rac1 = Rac Family Small GTPase 1; TGF = transforming growth factor.

function to prevent nephropathy or for CKD patients to avoid progression has not been addressed thus far in any guidelines.

5. OPTIMAL BP MAINTENANCE AGAINST HYPERTENSIVE NEPHROPATHY

Whether to target systolic BP <140 mmHg for renal protection remains uncertain. BP targets to curb renal injury are also dependent on the baseline renal preserve. Evidence of BP control for patients with fair kidney function is predominantly yielded from trials which only enrolled these subjects with the initial objective to study cardiovascular prevention. Kidney function was frequently documented to match characteristics to perform stratified analyses, and not for elucidating the renal prognosis. Studies which solely enrolled otherwise healthy individuals to investigate the impact of BP on renal function are scarce. Our previous study enrolled 351 nondiabetic patients with fair renal function and proposed an optimal office BP cutoff at 140/90 mmHg on the initial encounter and 130/80 mmHg for subsequent maintenance,[34] which significantly reduced major and minor renal events, that is, 50% and 25% eGFR decline from baseline, respectively.

For patients with baseline renal insufficiency, the goal of BP control remains elusive. Extensive research efforts have been made to determine the BP control target in the cohorts with CKD. Early in the last century, Modification of Diet in Renal Disease (MDRD) trial was designed to investigate optimal BP goals. The study enrolled 840 nondiabetic subjects with CKD and reported that intense BP control at mean arterial pressure <65 mmHg as compared with standard care yielded no significant efficacy against CKD progression. However, the follow-up duration was rather short.[35] Minutolo et al[36] noted that patients with CKD who kept ambulatory daytime BP <135/85 mmHg and nighttime BP <120/70 mmHg had better performance on composite renal outcomes. Stratified analysis of AASK patients with daily proteinuria >1g showed that these patients had greater renal preservation when maintaining mean arterial pressure <92 mmHg compared with <107 mmHg.[37] A total of 2646 subjects with underlying CKD from SPRINT trial were randomly assigned to undergo intense or standard BP control, which maintained systolic BP at 140 and 120 mmHg, respectively. Interestingly, although compromise of kidney function was more pronounced in rigorous arm during the first half year, a comparative incidence of renal events (≥50% eGFR decline) at 3.3 years follow-up was documented.[38] Thus far, evidence suggests targeting BP <130/80 mmHg as a practical goal in CKD patients for reduced mortality rates, and more intensive management may be necessary in the presence of concomitant proteinuria.[39]

Furthermore, baseline renal profile influences the effect of nephroprotection. Appel et al[40] reported those with initial protein-to-creatinine ratio >0.22 benefited more from intense BP control at 131/78 mmHg in an African American cohort. These studies raise the concern that current guideline recommendations exert insufficient renal protective effects especially for patients who already have hypertensive nephropathy, as strict BP management may sacrifice renal function in the long term (Table 3). In conjunction with high BP variability among this cohort, targets for home BP control to tailor the use of antihypertensive agents are urgently needed.

6. RENAL EFFECT OF DIFFERENT ANTIHYPERTENSIVE AGENTS

Antihypertensive agents are traditionally known to influence renal physiology. The mechanism of action to control BP differs, and so does the kidney impact. Diuretics are a classic example, which have been well established to hazard renal function in general population. In individuals with CKD, diuretics were demonstrated to decrease GFR and cause electrolyte imbalance in a dose-dependent manner.[41] As for patients with heart failure, early trials suggested the administration of diuretics did not predispose patients to rapid renal failure,[42] although it elevated the risk of renal function deterioration.[43] The slight difference in GFR decline was, however, considered unrelated to clinical outcome.[44] Diuretics are known to potentiate the effect of RAAS blockade. ACE inhibitors and ARBs have been well established to compromise intraglomerular perfusion, causing an elevation in serum creatinine. Amelioration of CKD progression and proteinuria by burden relief dominates in the long run.[45] As for beta-blockers (BB), nonselective BBs attenuate renal vascular resistance, leading to compromised renal hemodynamics. On the other hand, the vasodilating BBs which additionally antagonizes α1-receptor may preserve renal perfusion.[46] Finally, the influence of calcium channel blockers on renal

Table 3

Evidence of each office BP control target and guideline recommendations

BP target	Evidence	Ref
<130/80 mmHg	Decrease albuminuria risk but not ESRD (44 989 individuals from 19 trials, mean follow-up 3.8 y)	23
	Reduced albuminuria in non-Blacks with baseline heavy proteinuria (8 127 patients from 9 trials, median follow-up 3.3 y)	24
	Eligible BP maintenance goal to reduce renal event in nondiabetic patients (351 nondiabetic Taiwanese, average follow-up 4.2 y)	37
	Decelerated CKD progression if initial protein-to-creatinine ratio >0.22 (1094 Blacks, follow-up 8.8-12.2 y)	40
<120/70 mmHg	As nighttime target for better renal prognosis in patients with CKD	36

Guideline recommendation

	BP target		
Guideline	General populations	With comorbidities	Ref
ISH, 2020	<130/80 mmHg (<140/80 mmHg in elderly)		28
ESC, 2018	120~130/70~79 mmHg if 18~65 y old	120~130/70~79 mmHg for 18~65-y-old patients with DM	29
	130~139/70~79 mmHg if ≥65 y old	130~139/70~79 mmHg for ≥65-y-old patients with DM	
		130~139/70~79 mmHg for patients with CKD regardless of age	
AHA, 2017	<130/80 mmHg		30
TSOC, 2015	<140/90 mmHg (<150/90 mmHg if ≥ 80 y old)	<130/80 mmHg for hypertensive patients with DM, coronary heart disease, CKD with proteinuria, or under antithrombotics	32
		<140/90 mmHg for hypertensive patients with CKD	

The respective evidence of two widely adapted BP cutoff targets and their indicating population according to guideline recommendation are outlined.

AHA = American Heart Association; BP = blood pressure; CKD = chronic kidney disease; DM = diabetes mellitus; ESC = European Society of Cardiology; ESRD = end-stage renal disease; ISH = International Society of Hypertension; TSOC = Taiwan Society of Cardiology.

function is attributed to the suppression of platelet-derived growth factors and platelet-activating factors. New evidence also noted that dihydropyridinic calcium channel blockers exert renal-protective effects by altering glomerular pressure.[47] Different classes of BP medications respectively reshaped renal physiology.

7. POTENTIAL ROLE OF SODIUM GLUCOSE COTRANSPORTER 2 INHIBITOR FOR HYPERTENSIVE NEPHROPATHY

Sodium glucose cotransporter 2 (SGLT2) inhibitors were originally designed as antidiabetic agents but have gradually become a standard medication for heart failure. Literature also suggests that SGLT2 inhibitors lower BP.[48] Moreover, the percentage of individuals with renal impairment in trials was comparative to real word data, which allows for generalization of the renal effects. In Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients, Canagliflozin Cardiovascular Assessment Study, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58, and Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial, better renal composite endpoints, including kidney dysfunction, ESRD, the abundance of albuminuria, and renal death, were documented. For patients with underlying renal impairment, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease trials analyzing 4304 patients with CKD affirmed the renal-protective effects of dapagliflozin in this population.[49] The Study of Heart and Kidney Protection With Empagliflozin trial is also ongoing to substantiate such pleotropic efficacy. Although the detailed mechanism of renal protection by SGLT2 inhibitors remained elusive, Giorgino et al[50] summarized in terms of hemodynamic and metabolic factors. The former referred to natriuresis, osmotic diuresis, anti-inflammation, and ketone body formation. The later featured body weight and fat mass loss, which abated insulin resistance. National Kidney Foundation also endorses that the renal protective effect of SGLT2 inhibitors is not related to glycemic control.[51] A recent meta-analysis pooling 38 723 participants with DM further demonstrates that SGLT2 inhibitors significantly reduce the risk of renal failure.[52] SGLT2 inhibitors have been shown to induce both cardiovascular and renal benefits in various clinical backgrounds.

8. FUTURE PERSPECTIVES

Existing literature has consolidated the concept that poorly managed BP directly impacts renal function, although the clinical targets for BP control are currently undetermined in current guidelines. We herein pinpointed office BP at 130/80 mmHg as maintenance target for both otherwise healthy subjects and CKD patients for renal protection, with an upper threshold of 140/90 mmHg at the initial encounter for patients with preserved kidney function at baseline. Future prospective trials are warranted to solidify the evidence on renal prognosis in the cohorts with different BP characteristics and how their BP is controlled.

Because BP levels are greatly variable especially in patients with impaired renal function, how to accurately record BP levels and avoid masked or white coat hypertension are important cornerstones to address to study the hemodynamic impacts on renal prognosis. Gorostidi et al[53] examined 5693 Spanish patients with concurrent hypertension and CKD. Performance of BP control was surprisingly misclassified in one-third of the cohort.[53] Ku et al[54] also addressed the importance of accurate BP recording especially in a CKD cohort. Home recording was proposed to be an eligible approach to document BP performance, although 24-hour ambulatory BP monitoring is preferred, as it is better correlated with cardiac and renal outcome. Further, 24-hour ambulatory BP monitoring also provides prognostic values especially in patients with CKD,[55] and appears to be an appropriate method to study the holistic impact and physiology of hypertensive nephropathy, although the pragmatic considerations hamper its usage. Incorporating BP surveillance into daily living is of significant clinical importance.

In conclusion, hypertension is a common comorbidity with kidney disease, and poorly controlled BP exacerbates the progression of renal dysfunction. The literature regarding the hemodynamic impact of arterial pressure on nephropathy have not only reshape the understanding of "hypertensive nephropathy" but also create a need to determine a clinically feasible goal for BP control and maintenance. Office BP 130/80 mmHg has thus far been established to be the threshold for patients with underlying kidney dysfunction, while office BP 140/90 mmHg at the first visit may be acceptable for otherwise healthy individuals. Future trials of more intense BP targets are underway to delineate the renal prognosis and are expected to modify current guideline recommendations. SGLT2 inhibitors have also emerged as novel pharmaceutical options against hypertensive nephropathy. Meanwhile, the development of other modalities to longitudinally document daily BP levels will supplement office recording as more reliable references, with which better BP control can be realized.

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