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HYPERTENSION (DS GELLER AND DL COHEN, SECTION EDITORS)

Masked Hypertension in CKD: Increased Prevalence and Risk for Cardiovascular and Renal Events

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Abstract

Purpose of Review Hypertension and chronic kidney disease (CKD) are inextricably linked. The causal nature of the relationship is bidirectional. This relationship holds when blood pressure is assessed in the clinic and outside the clinic with home and ambulatory blood pressure monitoring. Patients with CKD are more likely to have high-risk hypertension phenotypes, such as masked and sustained hypertension, and are at increased risk for cardiovascular disease. The purpose of this review is to describe the increased prevalence of masked hypertension in patients with CKD and then describe the increased risk for target organ damage and adverse clinical events associated with masked hypertension in patients with CKD.

Recent Findings The prevalence of masked hypertension is greater in patients with CKD than that of the general population. Recent studies have demonstrated that masked hypertension is associated with increased risk for target organ damage including left ventricular hypertrophy, elevated pulse wave velocity, proteinuria, and decreased estimated glomerular filtration rate in patients with CKD. Additionally, in patients with CKD, masked hypertension is associated with increased risk for cardiovascular disease, end-stage renal disease, and all-cause mortality.

Summary Patients with CKD are at increased risk for masked hypertension. Masked hypertension is associated with increased risk for target organ damage and adverse cardiovascular and renal outcomes in patients with CKD. Further research is necessary to better understand the pathophysiology of masked hypertension, the optimal method for diagnosing masked hypertension, and to determine whether masked hypertension is a modifiable risk factor.

Keywords Hypertension · Chronic kidney disease · Cardiovascular disease · Masked hypertension · Ambulatory blood pressure monitoring

Introduction

Hypertension is a modifiable cardiovascular risk factor and has a bidirectional relationship with chronic kidney disease (CKD). CKD leads to hypertension through increased sodium retention, increased sympathetic tone, and endothelial dysfunction. As many as 86% of patients with CKD have hypertension [1, 2]. The impact of untreated hypertension on renal function is governed by a variety of factors, but can damage kidneys by causing glomerular sclerosis [3] and arteriolar nephrosclerosis [4]. Among CKD patients, higher systolic blood pressure (BP) has been shown to increase the risk of end-stage renal disease (ESRD), even after adjusting for other risk factors [5]. In fact, hypertension is a major risk factor for the development of chronic kidney disease (CKD) [6] and the second leading cause of ESRD in the USA [7].

The risk of cardiovascular disease associated with hypertension is higher among CKD patients [6, 8]. Maintaining target BP reduces the risk for cardiovascular events [9]. However, strict BP control does not delay the onset of ESRD [10]. The SPRINT demonstrated that targeting a systolic BP < 120 mmHg significantly reduced the risk of death and cardiovascular events when compared with a target of < 140 mmHg for non-diabetic adults. But among subjects with

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CKD at baseline, there was no meaningful difference in the likelihood of experiencing significant deterioration in kidney function (a decrease in estimated glomerular filtration rate [eGFR] > 50%) or ESRD associated with the more intensive BP target [11]. However, it is worth noting that the SPRINT CKD population was at low risk for progression of CKD given the mild CKD at baseline (eGFR ~ 72 ml/min/1.73 m^2) and the low level of proteinuria (urine albumin to creatinine ratio of ~ 43 mg/g). Additionally, there was a greater masked effect in the intensive treatment arm than in the standard treatment arm when assessed by 24-h ambulatory BP monitoring (ABPM) [12]. These results demonstrate the masked hypertension may be of greater clinical significance when more aggressive clinic BP targets are utilized.

Recent reviews have described the factors and patient characteristics associated with increased prevalence of masked hypertension as well as the association between masked hypertension and adverse outcomes in the general population [13, 14]. Additionally, a recent editorial outlined the important knowledge gaps in diagnosing and managing masked hypertension [15]. In this review, we describe the increased prevalence of masked hypertension in patients with CKD and then describe the increased risk for target organ damage and adverse clinical events associated with masked hypertension in patients with CKD.

Masked Hypertension

In clinical practice, a diagnosis of hypertension has typically been based on BP measurements in a clinic setting. The large majority of hypertension-related observational studies and nearly all randomized controlled trials have utilized clinic-based BP to define both hypertension and the target BP.

However, it is well known that several factors can influence manual BP readings and that clinic-based BPs reported in studies are a result of BP measurement techniques that do not adhere to recommended guidelines for measuring BP (Muntner, JACC, in press). As a result, patients who are otherwise normotensive may present with an elevated clinic-based BP ("white-coat" hypertension), while others who are, in fact, hypertensive can have clinic-based BPs within the normal range ("masked" hypertension). In order to "unmask" these phenomena, ambulatory blood pressure monitoring (ABPM) can be used to obtain out-of-office BP measurements throughout the day and night [16]. While ABPM is the preferred method for diagnosing masked hypertension because it provides an estimate of nighttime BP, home BP is an acceptable alternative [13]. The United States Preventative Services Task Force (USPSTF) and the 2017 ACC-AHA guidelines recommend out-of-office BP measurement to confirm the diagnosis of hypertension prior to treatment [17, 18••]. Interestingly, the USPSTF recommendation was based solely on the concern for over-treatment of white-coat hypertension and did not address the potential increased risk for adverse outcomes with masked hypertension that will be discussed in this review.

Recommended thresholds for clinic and out-of-office BP for defining the various hypertension phenotypes are as follows:

1. Normal (or controlled hypertension) is defined by a clinic BP < 130/80 mmHg and either home BP < 130/80 mmHg or 24-h ABPM < 125/75 mmHg,
2. White coat hypertension is defined by a clinic BP ≥ 130/80 mmHg and either home BP < 130/80 mmHg or 24-h ABPM < 125/75 mmHg,
3. Masked hypertension is defined by a clinic BP < 130/80 mmHg and either home BP ≥ 130/80 mmHg or 24-h ABPM ≥ 125/75 mmHg,
4. Sustained hypertension is defined by a clinic BP ≥ 130/80 mmHg and either home BP ≥ 130/80 mmHg or 24-h ABPM ≥ 125/75 mmHg [18••].

Increased Prevalence of Masked Hypertension in CKD

Masked hypertension is typically seen in about 8–20% of the general population who are not on antihypertensive therapy [19–22]. A meta-analysis of 36 studies incorporating 25,629 patients estimated the prevalence of masked hypertension to be about 19% among adults [23]. The prevalence of masked hypertension is likely higher in patients with CKD. Among 1492 participants with CKD in the Chronic Renal Insufficiency Cohort (CRIC) study, 28% had masked hypertension [24]. Similarly, in the Chronic Kidney Disease Japan Cohort (CKD-JAC), masked hypertension was present in 31% of participants [25]. In 617 participants from the African American Study of Kidney Disease and Hypertension (AASK) cohort, 25% had masked hypertension when defined by daytime ambulatory BP but as many as 43% had masked hypertension when both daytime and nighttime ambulatory BPs were considered [26]. It is worth noting that results are not entirely consistent; an earlier meta-analysis by Bangash and Agarwal found that only 8% of patients with CKD had masked hypertension [27]. Additionally, race and ethnicity may be associated with the prevalence of masked hypertension. In the International Database of Ambulatory BP in Renal Patients (I-DARE) study, when compared with CKD-JAC participants, those from AASK were more likely to have masked hypertension while participants from CRIC, Italy, and Spain were less likely to have masked hypertension [28]. In summary, the prevalence of masked hypertension is significant and likely greater in patients with CKD, although prevalence estimates vary and can differ by patient characteristics.

Masked Hypertension and Target Organ Damage

Studies of the general population reveal that masked hypertension is associated with increased cardiovascular target organ damage [21, 22, 29, 30]. Similar results have been observed in studies of patients with CKD. In the AASK cohort, participants with masked hypertension were more likely than those with normal BP and white-coat hypertension to have left ventricular hypertrophy (70% vs 54% and 50% in those with normal BP and white-coat hypertension, respectively) [26]. In the CRIC study, masked hypertension was associated with greater left ventricular mass index (2.52 $g/m^{2.7}$ higher, 95% CI 0.9 to 4.1) and pulse wave velocity (0.92 m/s higher, 95% CI 0.5 to 1.3) compared with those with controlled clinic and ambulatory BP [24]. In a cohort of patients with CKD from China, Tang et al. found that patients with masked hypertension were more likely to have left ventricular hypertrophy than those with normotension [31]. Masked hypertension is associated with cardiovascular target organ damage in patients with and without CKD.

In addition to cardiovascular target organ damage, masked hypertension is associated with greater proteinuria and reduced eGFR in the general population and in patients with CKD. Masked hypertension was associated with increased risk for CKD among 1023 residents in Ohasama, Japan [32]. In the AASK cohort, participants with masked hypertension were more likely than those with normal BP and white-coat hypertension to have a urinary protein:creatinine ratio > 0.22 mg/g [26]. In the CRIC study, masked hypertension was associated with lower eGFR and higher levels of proteinuria compared with those with controlled clinic and ambulatory BP [24]. Whether masked hypertension causes renal target organ damage or whether CKD leads to masked hypertension is difficult to ascertain. Patients with low eGFR and proteinuria are more likely to have a non-dipping pattern with elevated nighttime BP [33]. Additionally, a study of BP during and after exercise demonstrated that patients with masked uncontrolled hypertension and CKD had delayed recovery of exercise-induced hypertension compared with healthy controls [34]. In summary, masked hypertension is associated with renal target organ damage. Given the increased prevalence of masked hypertension in patients with CKD and the increased risk for cardiovascular disease in patients with CKD, future studies evaluating mechanisms underlying masked hypertension and treatment strategies targeting masked hypertension should focus on or at least include patients with CKD.

Masked Hypertension and Adverse Clinical Events

Masked hypertension is associated with cardiovascular and renal events as well as all-cause mortality. This has been demonstrated in a number of studies in the general population. Most recently, in an analysis of 63,910 Spanish patients with ABPM, compared with patients with normotension, risk for all-cause mortality was increased in those with masked hypertension (HR 2.83, 95% CI 2.12 to 3.79) and those with masked uncontrolled hypertension (HR 1.96, 95% CI 1.50 to 2.56). Similar results were observed for cardiovascular mortality [35••]. In the Jackson Heart Study, masked hypertension was present in 53% of participants and was associated with the development of CKD (adjusted OR 1.95, 95% CI 1.04 to 3.67) [36]. Fewer studies have evaluated the association between masked hypertension and adverse outcomes in patients with CKD. Kushiro et al. investigated the relationship between morning home systolic BP and clinic systolic BP and cardiovascular risk in hypertensive patients with or without CKD receiving olmesartan-based antihypertensive therapy using data from the HONEST study [37]. CKD patients were found to have a higher rate of cardiovascular events than non-CKD patients. Masked hypertension was associated with increased risk for a major cardiovascular event in patients with and without CKD [37].

Two studies have evaluated the association between masked hypertension and adverse clinical events in cohorts of patients with CKD. Minutolo et al. evaluated the association between masked hypertension and adverse clinical events in a cohort of 489 hypertensive patients with CKD. Fifteen percent of patients had masked hypertension. Over a median follow-up of 5.2 years, patients with masked hypertension were at increased risk for a cardiovascular composite of fatal and non-fatal myocardial infarction, congestive heart failure, stroke, revascularization, peripheral vascular disease, and non-traumatic amputation (HR 3.17, 95% CI 1.5 to 6.7) [38]. Patients with masked hypertension were also at increased risk for ESRD (HR 3.93, 95% CI 1.8 to 8.7) and all-cause mortality (HR 3.45, 95% CI 1.5 to 7.9) [38]. Similar results were observed in a cohort of CKD patients from China [39]. Compared with patients with normotension, patients with masked hypertension were at increased risk for all-cause mortality, renal events, and major adverse cardiovascular events [39].

While not specifically focused on masked hypertension per se, other studies of patients with CKD have evaluated the risk for adverse outcomes with elevated out-of-office BP after adjusting for clinic BP or in patients with controlled clinic BP. Home and clinic BPs were measured in a prospective cohort study of 217 Veterans with CKD [5]. Over a median follow-up of 3.5 years, a one standard deviation increase in home systolic BP was associated with an increased risk for ESRD (HR 1.74, 95% CI 1.04 to 2.93) in a model adjusting for clinic systolic BP and other risk factors. Similarly, elevated ambulatory BP was associated with increased risk for ESRD (HR 2.20, 95% CI 1.4 to 3.4) after adjusting for clinic systolic BP but the association was no longer significant after adjusting for other factors such as proteinuria and eGFR

[40]. In the same cohort, 24-h ambulatory BP (HR 2.22, 95% CI 1.2 to 4.0) but neither clinic (HR 1.08, 95% CI 0.5 to 2.2) or home (HR 1.36, 95% CI 0.7 to 2.8) BP was associated with risk for cardiovascular outcomes [41]. In the AASK study, ambulatory and clinic systolic BP was associated with renal and cardiovascular events [42]. However, after controlling for clinic BP, elevated ambulatory BP was only associated with renal outcomes in participants with clinic systolic BP < 130 mmHg (interaction $P < 0.05$) [42]. These studies demonstrate that an elevated out-of-office BP is a risk factor for adverse renal and cardiovascular events in patients with CKD, independent of clinic BPs.

Treatment of Masked Hypertension

The 2017 ACC-AHA guidelines recommend assessment of out-of-office BPs to detect masked hypertension and masked uncontrolled hypertension [18••]. This recommendation is based on the observational evidence of increased risk for adverse outcomes in these patients but does acknowledge, "there are no data on the risks and benefits of treating white coat and masked hypertension." Fortunately, there are ongoing trials evaluating whether treatment of masked hypertension is safe and effective. The MASTER (Masked Uncontrolled Hypertension Management Based on Office BP or on Out-of-Office [Ambulatory] BP Measurement) trial will enroll 1240 participants with masked uncontrolled hypertension and evaluate the effect of office or ambulatory BP based therapy on cardiac and renal target organ damage (ClinicalTrials.gov NCT02804074).

Conclusions

Hypertension and CKD are inextricably linked. Not surprisingly, the prevalence of masked hypertension is increased in patients with CKD. Masked hypertension is associated with renal and cardiovascular target organ damage in patients with CKD. Additionally, while not as well established as in the general population, masked hypertension is associated with adverse cardiovascular and renal outcomes as well as increased risk for all-cause mortality in patients with CKD. Recent guidelines have stressed the importance of out-of-office BPs in the diagnosis and treatment of patients with hypertension. Future studies are needed to identify patients most likely to have elevated out-of-office BPs so that clinicians can appropriately target home and ambulatory BP monitoring to high-risk patients. Finally, randomized controlled trials are needed to determine whether masked hypertension is a modifiable risk factor.

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Compliance with Ethical Standards

Conflict of Interest Megha Babu and Paul Drawz declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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