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Discrepancies in Clinic and Ambulatory Blood Pressure in Korean Chronic Kidney Disease Patients

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Blood pressure (BP) control is considered the most important treatment for preventing chronic kidney disease (CKD) progression and associated cardiovascular complications. However, clinic BP is insufficient to diagnose hypertension (HT) and to monitor overall BP control because it does not correlate well with ambulatory blood pressure monitoring (ABPM). We enrolled 387 hypertensive CKD patients (stages G1–G4, 58.4% male with median age 61 years) from 3 hospitals in Korea. HT of clinic BP and ABPM was classified as ≥ 140/90 and ≥ 130/80 mmHg, respectively. Clinic BP control rate was 60.2%. The median 24-hour systolic blood pressures (SBPs) of CKD G3b and CKD G4 were significantly higher than those of CKD G1–2 and CKD G3a. However, the median 24-hour SBPs were not different between CKD G1–2 and CKD G3a or between CKD G3b and CKD G4. Of all patients, 5.7%, 38.0%. 42.3%, and 14.0% were extreme-dippers, dippers, non-dippers, and reverse-dippers, respectively. Non-/reverse-dippers independently correlated with higher Ca × P product, higher intact parathyroid hormone (iPTH), and lower albumin. Normal BP was 33.3%, and sustained, masked, and white-coat HT were 29.7%, 26.9%, and 10.1%, respectively. White-coat HT independently correlated with age ≥ 61 years and masked HT independently correlated with CKD G3b/G4. In conclusion, ABPM revealed a high prevalence of non-/reverse-dippers and sustained/masked HT in Korean CKD patients. Clinicians should try to obtain a CKD patient's ABPM, especially among those who are older or who have advanced CKD as well as those with abnormal Ca × P product, iPTH, and albumin.

Keywords: Ambulatory Blood Pressure Monitoring; Blood Pressure; Chronic Kidney Disease; Hypertension; Masked Hypertension; White-Coat Hypertension

INTRODUCTION

Chronic kidney disease (CKD) is a major health problem, and it affects ~10% of adults in Western countries (1). In Korea, CKD prevalence was 7.8% overall (Korea National Health and Nutrition Examination Survey [KNHANES] data) and 13.7% in urban population with age ≥ 35 years in Korea (2,3). Among various risk factors, hypertension (HT) is considered an important one in the development and progression of CKD (4). HT also increases the risk of death and cardiovascular disease (5).

To reduce these risks, recent guidelines recommend strict control of blood pressure (BP) to ≤ 130/80 and ≤ 140/90 mmHg in CKD patients with and without proteinuria, respectively (4,6). However, a large proportion of CKD patients have inadequate BP control, and the proportions vary from report to report (7,8). Furthermore, BP may not be properly controlled in many Korean CKD patients. In Korea, KNHANES guidelines suggested that 58.5% of the general population had appropriate clinic BP (< 130/80 mmHg), and an Assessment of Blood Pressure Control and Target Organ Damage in Patients with Chronic Kidney Disease and Hypertension (APrODiTe) study reported that 53.4% of CKD patients had controlled clinic BP (< 140/90 mmHg) (9,10). Furthermore, it is important to increase the BP control rate as kidney function deteriorates. The National Kidney Foundation-Kidney Early Evaluation Program (NKF-KEEP) in the United States reported that rates of HT awareness, treatment, and adequate HT control increased progressively with advancing kidney disease despite increasing HT prevalence (11). Unfortunately, this aspect of BP control is not known in Korean CKD patients.

Clinic BP is considered insufficient to diagnose HT and monitor overall BP control because it does not correlate well with ambulatory blood pressure monitoring (ABPM), which encompasses white-coat or masked HT (12,13). CKD is associated not only with an abnormal dipping pattern but also with white-coat or masked HT (7,10,14-19). These abnormal ABPM patterns are considered to be associated with cardiovascular disease and CKD progression (20).

We conducted a multicenter, cross-sectional study to examine BP control status and patterns and dipping patterns in Korean CKD patients. We also investigated clinical characteristics

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associated with abnormal BP patterns.

MATERIALS AND METHODS

Study population

From August 2014 to May 2015, patients with HT and CKD stages G1–G4 treated at the Seoul National University Boramae Medical Center, Seoul National University Hospital, and Seoul National University Bundang Hospital were enrolled. The inclusion criteria were as follows: 1) age of 20–75 years, 2) BP ≥ 140/90 mmHg, and/or 3) taking the same BP medication since at least 2 weeks before enrollment. Patients with acute kidney injury, hospitalization, renal replacement therapy, previous kidney transplantation, uncontrolled arrhythmia, asthma, chronic obstructive pulmonary disease, and primary endocrine disorders except diabetes mellitus were excluded. Pregnant women and anyone who worked night shifts were also excluded.

Definitions

CKD is defined by the Kidney Disease Improving Global Outcomes (KDIGO) as abnormalities of kidney structure or function that are present for at least 3 months (4). CKD stages were defined according to glomerular filtration rate (GFR) categories as defined by KDIGO guidelines (4). The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease-Epidemiology Collaboration equation (21). Serum creatinine (Cr) was measured using the isotope dilution mass spectrometry-traceable method. Extreme-dippers were defined as patients having a nighttime/daytime systolic blood pressure (SBP) ≤ 0.8; dippers, as those with a ratio of 0.8–0.9; non-dippers, as those with a ratio of 0.9–1.0; and reverse-dippers, as those with a ratio > 1.0 (22). HT as diagnosed by clinic BP and ABPM measurements was ≥ 140/90 and ≥ 130/80 mmHg, respectively. Normal BP was defined as both normal clinic BP and ABPM; sustained HT, as both HT clinic BP and ABPM; white-coat HT, as a HT clinic BP and normal ABPM (12); and masked HT, as normal clinic BP and HT ABPM (13).

Clinic BP measurement

Clinic BP was measured by trained medical staff using a mercury sphygmomanometer with an appropriately sized cuff (23). All participants rested over 5 minutes and were prohibited from smoking and ingesting caffeine for 30 minutes before measurements. Three measurements were performed at 1-minute intervals, and the average of the last 2 measurements was taken as the clinic BP.

ABPM

Patients underwent 24-hour ABPM using Oscar 2 (SunTech Medical, Morrisville, NC, USA) and Mobile-O-Graph (I.E.M. GmbH, Stolberg, Germany). BP monitoring was performed on a typical work day. BP was recorded every 30 minutes. The ABP reading was considered adequate if the monitor had been worn for 24-hour and there were more than 16 acceptable readings between 8 AM and 10 PM (daytime) and more than 12 acceptable readings between 10 PM and 8 AM (nighttime).

Baseline demographics and clinical characteristics

Demographic characteristics, CKD causes, medical history, and laboratory data such as hemoglobin (Hb), albumin, blood urea nitrogen (BUN), Cr, calcium (Ca), phosphorus (P), intact parathyroid hormone (iPTH), total cholesterol (Total-C), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and random urine protein/Cr ratio (UPCR) were obtained at the baseline study visit. Comorbidities were evaluated using the modified Charlson Comorbidity Index Score (CCIS) (24).

Statistical analysis

Quantitative variables are presented as mean ± standard deviation (SD) for normally distributed variables. Non-parametric variables are expressed as median (range). Categorical variables are expressed as numbers with proportions. Quantitative variables were analyzed using analysis of variance (ANOVA) followed by the Bonferroni post-hoc test or the Kruskal-Wallis or Mann-Whitney rank sum tests for non-parametric variables. Chi-square tests were used to compare categorical variables. Simple logistic regression analysis was applied to find the unadjusted factors that correlated with dipping patterns and BP control patterns. Multiple logistic regression analysis with backward elimination technique adjusted for factors with $P < 0.05$ was used to identify independent predictors of dipping patterns and BP control patterns. The relationship between the 2 continuous variables was assessed by Pearson's correlation method. Statistical analysis was performed using IBM SPSS Statistics 20 (SPSS Inc., Chicago, IL, USA). P value < 0.05 was considered statistically significant.

Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Boramae Medical Center (26-2014-63), Seoul National University Hospital (1406-131-593), and Seoul National University Bundang Hospital (B-1408/262-403). Informed consent was submitted by all subjects when they were enrolled.

RESULTS

A total of 433 patients agreed to undergo ABPM, and 46 patients were excluded because they withdrew from the study or their ABPM measurements were not adequate. Finally, 387 CKD patients were enrolled in this study (Fig. 1).

Demographic and clinical characteristics according to CKD stages

Table 1 shows the general characteristics of the 387 patients. Of these, 226 patients (58.4%) were male, and their median age was 61 (20–75) years. Diabetic nephropathy, glomerulonephritis, hypertensive nephropathy, and polycystic kidney disease were reported in 141 (36.5%), 107 (27.6%), 80 (20.7%), and 9 (2.3%) patients, respectively. Of all patients, 95 (24.6%) were CKD G1–2, 79 (20.4%) were CKD G3a, 93 (24.0%) were CKD G3b, and 120 (31.0%) were CKD G4. Table 1 also shows the demographic and laboratory characteristics according to the CKD stages.

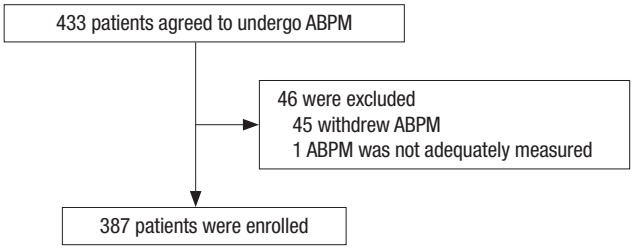

Fig. 1. Diagram of patients enrollment. A total of 433 CKD patients agreed to undergo ABPM, and 46 patients were excluded from the analysis.
CKD = chronic kidney disease, ABPM = ambulatory blood pressure monitoring.

The median clinic BP was 133 (90–207)/78 (30–115) mmHg. According to ABPM, the median 24-hour BP was 129 (94–207)/79 (49–114) mmHg, median daytime BP was 133 (94–213)/82 (52–115) mmHg, and median nighttime BP was 121 (87–197)/73 (42–117) mmHg. Of all patients, 233 (60.2%) had controlled clinic BP (< 140/90 mmHg), whereas 134 (34.6%) using ABP criteria had < 130/80 mmHg.

The median clinic, 24-hour, daytime, and nighttime SBPs were not different between CKD G1–2 and CKD G3a. The median 24-hour, daytime, and nighttime SBPs were not different between CKD G3b and CKD G4. The median clinic diastolic blood pressure (DBP) of CKD G1–2 (80 [60–115] mmHg) was significantly higher than that of CKD G3a (80 [58–105] mmHg, $P = 0.033$), CKD G3b (78 [40–108] mmHg, $P = 0.013$), and CKD G4 (75 [30–104] mmHg, $P = 0.001$). There were no differences in the 24-hour, daytime, and nighttime DBP between all CKD stages (Fig. 2).

Dipping patterns

Of all patients, 22 (5.7%) were extreme-dippers, 147 (38.0%) were dippers, 164 (42.3%) were non-dippers, and 54 (14.0%) were reverse-dippers. Reverse-dippers showed lower median eGFR and

Table 1. Demographic and clinical characteristics according to CKD stages

Variables	Total (n = 387)	CKD G1–2 (n = 95)	CKD G3a (n = 79)	CKD G3b (n = 93)	CKD G 4 (n = 120)	*P* value
Male	226 (58.4)	61 (64.2)	47 (59.5)	55 (59.1)	63 (52.5)	0.377
Age, yr	61 (20–75)	61 (24–74)	65 (20–74)	66 (23–75)	64 (27–75)	0.012
BMI, kg/m^2	25.1 ± 3.8	25.6 ± 3.8	24.5 ± 2.9	24.7 ± 4.3	25.3 ± 3.8	0.197
Diabetes mellitus	141 (36.5)	25 (26.3)	17 (21.8)	31 (33.3)	68 (56.7)	0.000
Current smoker	47 (12.1)	10 (10.6)	13 (16.5)	14 (15.1)	10 (8.3)	0.380
Alcohol	109 (28.4)	34 (36.2)	21 (26.6)	26 (28.0)	28 (23.3)	0.216
CCIS	4 (0–13)	4 (0–8)	4 (0–13)	5 (0–12)	5 (0–10)	< 0.001
BUN, mg/dL	24 (4–101)	15 (9–36)	20 (9–33)	25 (13–47)	36 (4–101)	< 0.001
Cr, mg/dL	1.57 (0.52–4.39)	0.96 (0.52–1.40)	1.32 (0.94–1.94)	1.78 (1.25–2.58)	2.51 (1.59–4.39)	< 0.001
eGFR, mL/min/1.73 m^2	40.2 (15.0–132.4)	72.8 (60.0–132.4)	50.2 (45.1–59.1)	36.5 (30.2–44.5)	22.7 (15.0–29.9)	< 0.001
Ca, mg/dL	9.1 (7.2–10.2)	9.1 (8.2–10.0)	9.2 (8.2–9.9)	9.2 (7.8–10.2)	8.9 (7.2–10.0)	< 0.001
P, mg/dL	3.6 (0.8–8.9)	3.5 (0.8–5.3)	3.4 (2.4–4.5)	3.5 (2.1–8.9)	3.9 (2.8–5.4)	< 0.001
Ca × P, mg^2/dL^2	32.9 ± 5.9	32.0 ± 6.1	31.2 ± 4.3	33.1 ± 7.0	34.7 ± 5.1	< 0.001
iPTH, pg/mL	42 (5–296)	28 (7–105)	28 (6–82)	41 (5–211)	71 (13–296)	< 0.001
UPCR, mg/mg	0.71 (0.03–16.73)	0.47 (0.04–6.35)	0.38 (0.03–12.78)	0.74 (0.03–14.73)	1.46 (0.06–16.73)	< 0.001
Total-C, mg/dL	168 ± 43	171 ± 41	173 ± 38	171 ± 40	160 ± 48	0.105
LDL-C, mg/dL	94 ± 35	97 ± 32	93 ± 32	94 ± 35	91 ± 39	0.743
HDL-C, mg/dL	48 (22–214)	48 (30–99)	46 (29–115)	45 (22–214)	42 (23–142)	0.011
TG, mg/dL	133 (30–1,180)	123 (51–669)	119 (47–334)	154 (49–1,180)	138 (30–437)	0.225
Hb, g/dL	12.9 ± 2.0	14.2 ± 1.7	13.5 ± 2.0	12.9 ± 1.9	11.4 ± 1.5	< 0.001
Albumin, g/dL	4.2 (2.3–5.0)	4.2 (2.8–4.8)	4.2 (3.5–5.0)	4.2 (2.3–4.8)	4.0 (2.6–4.8)	< 0.001
No. of drugs	2 (0–7)	2 (0–4)	2 (0–4)	2 (0–5)	2 (0–7)	0.007
CCB	240 (62.0)	55 (57.9)	45 (57.0)	62 (66.7)	78 (65.0)	0.415
ACEi/ARB	294 (76.0)	79 (83.2)	61 (77.2)	74 (79.6)	80 (66.7)	0.028
β-blocker	123 (31.8)	22 (23.2)	20 (25.3)	27 (29.0)	54 (45.0)	0.002
Diuretics	84 (21.6)	12 (12.6)	10 (12.7)	21 (22.6)	41 (34.2)	< 0.001

Values for categorical variables are given as a number (%); Values for continuous variables are given as mean ± standard deviation or median (range).
ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, BUN = blood urea nitrogen, Ca = calcium, CCB = calcium channel blocker, CCIS = modified Charlson Comorbidity Index Score, CKD = chronic kidney disease, Cr = creatinine, eGFR = estimated glomerular filtration rate, Hb = hemoglobin, HDL-C = high-density lipoprotein cholesterol, iPTH = intact parathyroid hormone, LDL-C = low-density lipoprotein cholesterol, No. = number, P = phosphorus, TG = triglyceride, Total-C = total cholesterol, UPCR = random urine protein/creatinine ratio.

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a higher proportion of CKD G3b/G4, but no statistically significant difference. Reverse-dippers showed higher median P (P = 0.001), TG (P = 0.020), and nighttime SBP (P < 0.001) and lower median albumin (P < 0.001) than extreme-dippers, dippers, and non-dippers. They also showed higher median UPCR than extreme-dippers and dippers (P = 0.028). Reverse-dippers showed

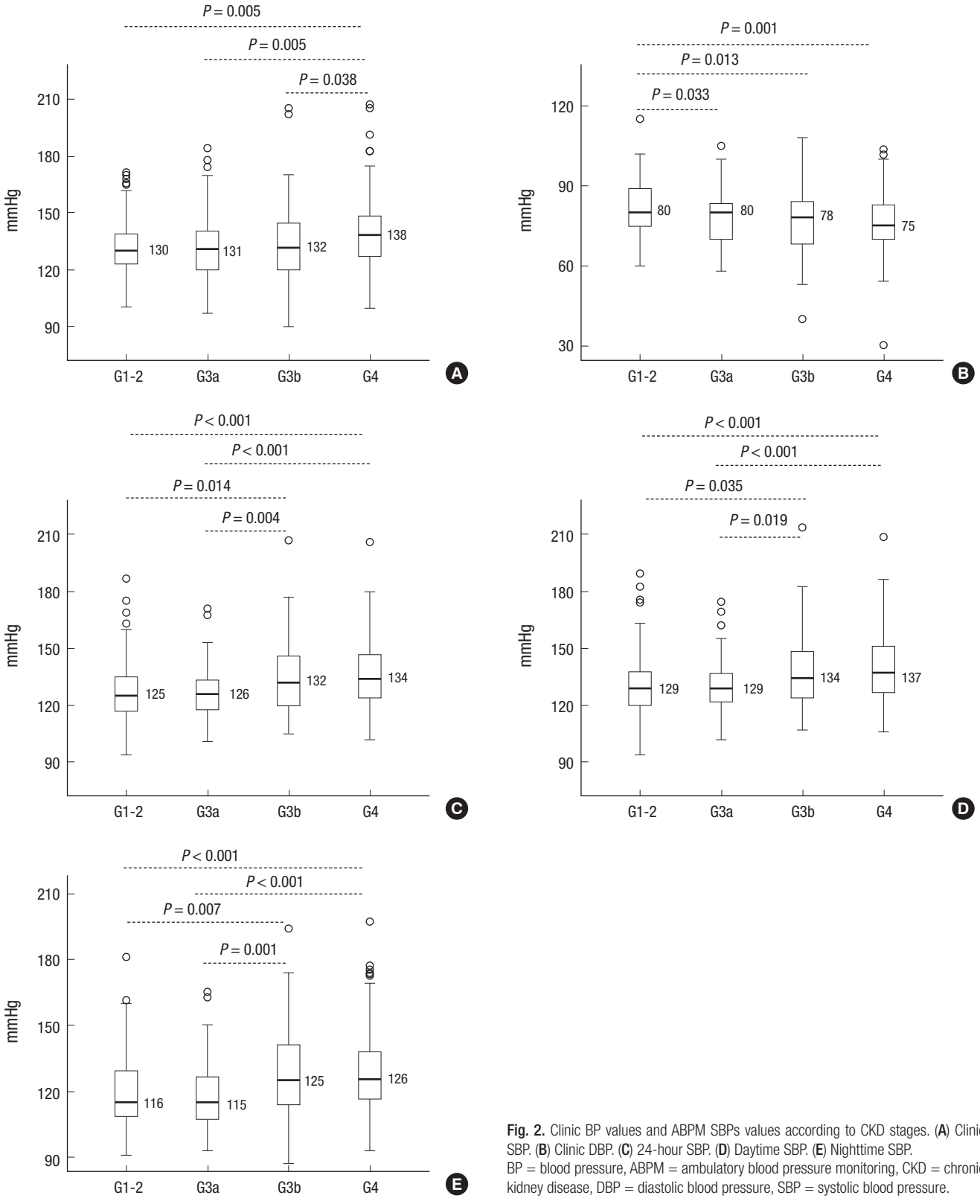

Fig. 2. Clinic BP values and ABPM SBPs values according to CKD stages. (**A**) Clinic SBP. (**B**) Clinic DBP. (**C**) 24-hour SBP. (**D**) Daytime SBP. (**E**) Nighttime SBP.
BP = blood pressure, ABPM = ambulatory blood pressure monitoring, CKD = chronic kidney disease, DBP = diastolic blood pressure, SBP = systolic blood pressure.

Table 2. Demographic, clinical, and BP characteristics according to dipping patterns

Variables	Extreme-dippers (n = 22)	Dippers (n = 147)	Non-dippers (n = 164)	Reverse-dippers (n = 54)	*P* value
Male	15 (68.2)	90 (61.2)	92 (56.1)	29 (53.7)	0.532
Age, yr	67 (50–74)	63 (32–74)	64 (23–75)	66 (33–75)	0.223
BMI, kg/m^2	25.1 ± 3.2	25.5 ± 3.2	25.6 ± 4.9	25.4 ± 3.7	0.662
Diabetes mellitus	9 (40.9)	52 (35.6)	55 (33.5)	25 (46.3)	0.378
Current smoker	3 (13.6)	16 (11.0)	23 (14.0)	5 (-9.3)	0.693
Alcohol	7 (31.8)	44 (30.1)	46 (28.0)	12 (22.2)	0.713
CCIS	5 (0–8)	5 (0–10)	4 (0–11)	5 (0–13)	0.070
BUN, mg/dL	21 (11–86)	24 (4–60)	25 (10–101)	27 (13–58)	0.154
Cr, mg/dL	1.52 (0.87–4.39)	1.53 (0.52–3.94)	1.67 (0.74–4.26)	1.77 (0.76–4.02)	0.426
eGFR, mL/min/1.73 m^2	37.4 (15.0–85.7)	41.2 (15.0–132.4)	36.4 (15.0–97.4)	32.3 (15.0–76.1)	0.430
CKD G3b/G4	10 (45.5)	77 (52.4)	90 (54.9)	36 (66.7)	0.242
Ca, mg/dL	9.0 (7.8–9.9)	9.0 (7.2–10.2)	9.1 (7.7–10.1)	9.1 (7.6–9.9)	0.902
P, mg/dL	3.4 (0.8–4.6)	3.6 (2.4–5.4)	3.6 (2.5–5.3)	3.9 (2.1–8.9)*,†,‡	0.001
Ca × P, mg^2/dL^2	31.8 ± 5.8	32.6 ± 5.5	32.7 ± 4.6	36.1 ± 10.0†,‡	< 0.001
iPTH, pg/mL	40 (20–167)	35 (13–157)	44 (7–239)	54 (14–296)	0.376
UPCR, mg/mg	0.45 (0.03–7.25)	0.60 (0.04–11.75)	0.74 (0.03–14.73)	1.07 (0.08–16.73)*,†	0.028
Total-C, mg/dL	149 ± 21	167 ± 39	167 ± 44	166 ± 48	0.467
HDL-C, mg/dL	47 (22–79)	45 (29–99)	45 (25–115)	46 (23–86)	0.432
LDL-C, mg/dL	77 ± 21	91 ± 31	94 ± 35	99 ± 44	0.517
TG, mg/dL	115 (65–259)	135 (51–669)	131 (30–1,180)	173 (35–409)*,†,‡	0.020
Hb, g/dL	12.8 ± 3.2	12.7 ± 2.0	12.6 ± 2.0	12.6 ± 2.2	0.542
Albumin, g/dL	4.3 (3.5–4.8)	4.2 (2.9–4.9)	4.2 (2.3–4.7)	4.0 (2.7–4.4)*,†,‡	0.011
No. of drugs	3 (1–4)	2 (0–7)	2 (0–5)	2 (1–4)	0.800
CCB	11 (50.0)	88 (59.9)	106 (64.6)	35 (64.8)	0.514
ACEi/ARB	17 (77.3)	114 (77.6)	123 (75.0)	40 (74.1)	0.938
β–blocker	6 (27.3)	49 (33.3)	51 (31.1)	17 (31.8)	0.939
Diuretics	5 (22.7)	28 (19.0)	35 (21.3)	16 (29.6)	0.452
Clinic SBP	141 (107–175)	135 (100–175)	134 (90–207)	138 (108–183)	0.769
Clinic DBP	76 (57–82)	77 (58–99)	76 (53–115)	73 (54–104)	0.183
24-hr SBP	140 (118–159)	129 (102–175)	131 (104–206)	139 (112–171)	0.072
24-hr DBP	79.0 ± 9.7	77.3 ± 10.5	80.0 ± 10.1	81.3 ± 10.6	0.282
Daytime SBP	149 (124–171)	135 (106–182)	133 (105–208)	139 (110–168)	0.054
Daytime DBP	84.1 ± 9.9	80.5 ± 10.7	81.0 ± 10.6	81.4 ± 11.0	0.328
Nighttime SBP	112 (99–136)	115 (93–160)	125 (100–197)*,†	144 (114–177)*,†,‡	< 0.001
Nighttime DBP	64.1 ± 8.5	69.2 ± 10.2	75.1 ± 10.1*,†	82.2 ± 12.2*,†,‡	< 0.001

Values for categorical variables are given as a number (%); Values for continuous variables are given as mean ± standard deviation or median (range).
ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, BP = blood pressure, BUN = blood urea nitrogen, Ca = calcium, CCB = calcium channel blocker, CCIS = modified Charlson Comorbidity Index Score, CKD = chronic kidney disease, Cr = creatinine, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, Hb = hemoglobin, HDL-C = high-density lipoprotein cholesterol, iPTH = intact parathyroid hormone, LDL-C = low-density lipoprotein cholesterol, No. = number, P = phosphorus, SBP = systolic blood pressure, TG = triglyceride, Total-C = total cholesterol, UPCR = random urine protein/creatinine ratio.
*Significant with extreme-dippers; †Significant with dippers; ‡Significant with non-dippers.

higher mean Ca × P product than dippers and non-dippers (P < 0.001) (Table 2).

The Ca × P product and iPTH positively correlated with nighttime/daytime SBP ratio (R^2 = 0.033, P < 0.001 and R^2 = 0.017, P = 0.011, respectively) (Fig. 3). The P, Ca × P product, iPTH, albumin, nighttime SBP, and nighttime DBP significantly correlated with the non-/reverse-dippers in univariate analyses. Multiple logistic regression analyses conducted with the above factors and eGFR showed that the Ca × P product (odds ratio [OR], 1.212; 95% confidence interval [CI], 1.041–1.411; P = 0.013), iPTH (OR, 1.008; 95% CI, 1.002–1.014; P = 0.013), and albumin (OR, 0.363; 95% CI, 0.174–0.761; P = 0.007) were independently associated with non-/reverse-dippers when BP data were not included. When multiple logistic regression analyses were performed with the above factors, eGFR, and BP data, the Ca × P product (OR, 1.247; 95% CI, 1.053–1.582; P = 0.011), nighttime SBP (OR, 1.042; 95% CI, 1.022–1.062; P < 0.001), and nighttime DBP (OR, 1.040; 95% CI, 1.010–1.070; P = 0.008) were independently associated with non-/reverse-dippers (Table 3).

BP control patterns

Among all patients, normal BP was most common (33.3%), followed by sustained HT (29.7%), masked HT (26.9%), and white-coat HT (10.1%). The median 24-hour SBP (P < 0.001), daytime SBP (P < 0.001), and nighttime SBP (P < 0.001) were the highest in sustained HT than in normal BP, white-coat HT, and masked HT. Masked HT showed higher ABPM SBPs than normal BP and white-coat HT (P < 0.001) (Table 4). However, clinic SBP was

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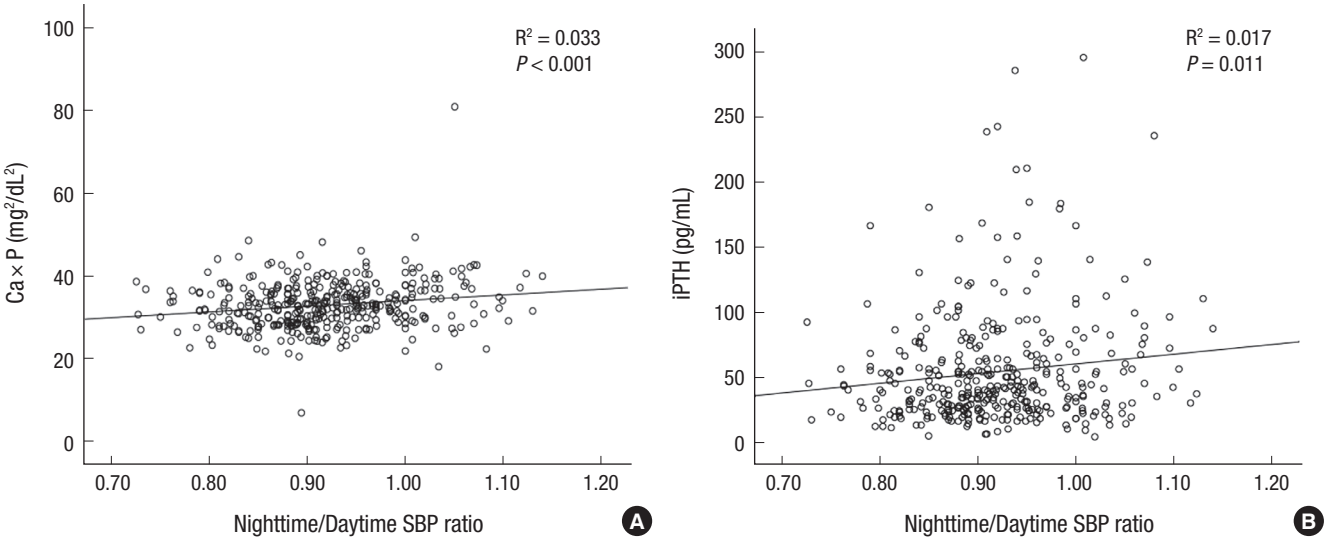

Fig. 3. Correlation of Ca × P and iPTH with nighttime/daytime SBP ratio. (**A**) Ca × P product. (**B**) iPTH.
Ca = calcium, P = phosphorus, iPTH = intact parathyroid hormone, SBP = systolic blood pressure.

Table 3. Factors related to non-/reverse-dippers

Factors	Model 1			Model 2		
	Multivariate OR	95% CI	*P* value	Multivariate OR	95% CI	*P* value
Ca × P (per 1 mg²/dL²)	1.212	1.041–1.411	0.013	1.249	1.053–1.482	0.011
iPTH (per 1 pg/mL)	1.008	1.002–1.014	0.013	-	-	-
Albumin (per 1 g/dL)	0.363	0.174–0.761	0.007	-	-	-
Nighttime SBP (per 1 mmHg)	-	-	-	1.042	1.022–1.062	< 0.001
Nighttime DBP (per 1 mmHg)	-	-	-	1.040	1.010–1.070	0.008

Model 1: adjusted for P, Ca × P, iPTH, albumin, eGFR, and UPCR; Model 2: adjusted for P, Ca × P, iPTH, albumin, eGFR, UPCR, nighttime SBP, and nighttime DBP.
Ca = calcium, CI = confidence interval, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, iPTH = intact parathyroid hormone, OR = odds ratio, P = phosphorus, SBP = systolic blood pressure, UPCR = random urine protein/creatinine ratio.

not different between sustained HT and white-coat HT (Table 4).

Normal BP showed lower median BUN ($P < 0.001$), Cr ($P < 0.001$), and CCIS ($P = 0.003$); higher median eGFR ($P < 0.001$) and HDL-C ($P = 0.007$); and lower proportion of DM ($P < 0.001$) and CKD G3b/G4 ($P < 0.001$) than sustained HT, white-coat HT, and masked HT. Normal BP also showed lower median iPTH ($P = 0.002$) and UPCR ($P = 0.001$) than sustained HT and masked HT. Sustained HT showed a higher proportion of DM ($P < 0.001$) and lower proportion of CKD G3b/G4 ($P < 0.001$) than masked HT. Sustained HT and masked HT showed lower median albumin ($P = 0.002$) than normal BP and white-coat HT. Sustained and masked HT patients were also prescribed more diuretics than those with normal BP ($P = 0.009$) (Table 4).

Multiple logistic regression analyses showed that age ≥ 61 years (OR, 0.601; 95% CI, 0.378–0.957; $P = 0.032$), Cr (OR, 0.352; 95% CI, 0.237–0.523; $P < 0.001$), and HDL-C (OR, 1.015; 95% CI, 1.002–1.928; $P = 0.012$) independently associated with normal BP. DM (OR, 1.921; 95% CI, 1.170–3.154; $P = 0.010$), Ca (OR, 0.585; 95% CI, 0.348–0.980; $P = 0.042$), and LDL-C (OR, 1.007; 95% CI, 1.000–1.014; $P = 0.037$) independently associated with sustained HT. Age ≥ 61 years (OR, 2.117; 95% CI, 1.035–4.331; $P = 0.040$) independently correlated with white-coat HT. CKD G3b/G4 (OR, 2.778; 95% CI, 1.695–4.552; $P < 0.001$) independently correlated with masked HT (Table 5).

DISCUSSION

This study demonstrated that the clinic BP control rate was 60.2%. The median 24-hour SBPs of CKD G3b and CKD G4 were significantly higher than those of CKD G1–2 and CKD G3a. However, the median 24-hour SBPs were not different between CKD G1–2 and CKD G3a or between CKD G3b and CKD G4. Of all Korean CKD patients, 56.3% were non-/reverse-dippers. Non-/reverse-dippers are associated with higher P, higher Ca × P product, and lower albumin. They also show high prevalence of sustained HT (29.7%) and masked HT (26.9%). Sustained HT correlated with DM, lower Ca, and higher LDL-C. White-coat HT was associated with age ≥ 61 years and masked HT was associated with CKD G3b/G4.

Many previous studies have reported on control of clinic BP in CKD patients. NKF-KEEP showed that 31.4% and 13.2% of patients maintained clinic BP ≤ 140/90 and 130/80 mmHg, re-

Table 4. Demographic, clinical, and BP characteristics according to BP control pattern

Variables	Normal BP (n = 129)	Sustained HT (n = 115)	White-coat HT (n = 39)	Masked HT (n = 104)	*P* value
Male	66 (51.2)	75 (65.2)	23 (59.0)	62 (59.6)	0.168
Age, yr	59 (20–75)†,‡	62 (31–75)	67 (24–74)	63 (21–75)	0.022
BMI, kg/m^2	25.1 ± 4.1	24.7 ± 3.5	25.5 ± 3.9	25.2 ± 3.7	0.703
Diabetes mellitus	29 (22.5)†,‡,§	58 (50.9)§	15 (38.5)	39 (37.5)	< 0.001
Current smoker	18 (14.1)	12 (10.4)	2 (5.1)	15 (14.4)	0.781
Alcohol	42 (32.8)	28 (24.3)	6 (15.4)	33 (31.7)	0.112
CCIS	3 (0–10)†,‡,§	4 (0–13)	5 (0–10)	4 (0–12)	0.003
BUN, mg/dL	20 (10–60)†,‡,§	25 (10–86)	25 (4–60)	26 (9–101)	< 0.001
Cr, mg/dL	1.27 (0.52–3.49)†,‡,§	1.68 (0.65–4.39)	1.77 (0.65–4.15)	1.83 (0.69–3.73)	< 0.001
eGFR, mL/min/1.73 m^2	53.4 (15.0–132.4)†,‡,§	38.4 (15.0–91.4)	33.3 (15.1–95.3)	36.3 (15.0–90.1)	< 0.001
CKD G3b/4	43 (33.3)†,‡,§	69 (60.0)§	26 (66.7)	75 (72.1)	< 0.001
Ca, mg/dL	9.1 (7.6–10.1)	8.9 (7.6–9.9)*,§	9.1 (7.9–9.9)	9.1 (7.2–10.2)	0.006
P, mg/dL	3.5 (0.8–5.3)	3.7 (2.1–5.4)	3.7 (2.6–4.9)	3.6 (2.3–8.9)	0.058
Ca × P, mg^2/dL^2	32.2 ± 5.4	33.0 ± 5.2	33.3 ± 4.4	33.3 ± 7.5	0.367
iPTH, pg/mL	35 (7–296)†,§	53 (12–243)	54 (13–185)	44 (5–286)	0.002
UPCR, mg/mg	0.48 (0.04–14.73)†,§	0.74 (0.03–16.73)	0.78 (0.03–9.00)	0.99 (0.08–7.02)	0.001
Total-C, mg/dL	168 ± 41	172 ± 41	156 ± 28	167 ± 50	0.173
HDL-C, mg/dL	51 (26–142)†,‡,§	47 (22–97)	46 (27–87)	46 (25–214)	0.007
LDL-C, mg/dL	91 ± 30	100 ± 40	84 ± 26	94 ± 36	0.061
TG, mg/dL	125 (47–440)	135 (56–1,180)	156 (51–318)	138 (30–817)	0.312
Hb, g/dL	13.2 ± 1.8	12.7 ± 2.3	12.3 ± 1.7	12.7 ± 2.0	0.027
Albumin, g/dL	4.3 (2.3–4.8)	4.1 (2.7–5.0)*,‡	4.3 (3.5–4.8)	4.1 (2.9–4.9)*,‡	0.002
No. of drugs	2 (0–5)	2 (0–5)	2 (0–4)	2 (0–7)	0.162
CCB	77 (59.7)	75 (65.2)	24 (61.5)	64 (61.5)	0.847
ACEi/ARB	101 (78.3)	85 (73.9)	28 (71.8)	80 (76.9)	0.784
β-blocker	43 (33.3)	40 (34.8)	8 (20.5)	32 (30.8)	0.399
Diuretics	18 (14.0)	34 (29.6)*,‡	5 (12.8)	27 (26.0)*	0.009
Clinic SBP	125 (90.0–139.5)†,‡,§	147 (117.0–207.0)	146 (112.0–178.0)	130 (100.0–139.5)‡	< 0.001
Clinic DBP	75 (54–89.5)†,‡	86 (30–115)‡	80 (56–99)	74 (53–89)†,‡	< 0.001
24-hr SBP	119 (94.0–129.5)‡	143 (113.0–207.0)*,‡,§	121 (105.0–129.0)	135 (112.0–171.0)*,‡	< 0.001
24-hr DBP	73.4 ± 6.1	85.5 ± 10.9*,‡	70.4 ± 7.0	83.3 ± 9.1*,‡	< 0.001
Daytime SBP	122 (9–142)‡	147 (111–213)*,‡,§	124 (108–135)	137 (114–175)*,‡	< 0.001
Daytime DBP	76.7 ± 7.9	88.0 ± 11.4*,‡	72.9 ± 7.4	85.0 ± 9.6*,‡	< 0.001
Nighttime SBP	111 (87–133)	134 (99–197)*,‡,§	113 (96–132)	128 (101–174)*,‡	< 0.001
Nighttime DBP	68.3 ± 8.2	79.2 ± 12.0*,‡	64.2 ± 8.1	77.9 ± 10.2*,‡	< 0.001

Values for categorical variables are given as a number (%); Values for continuous variables are given as mean ± standard deviation or median (range).
ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, BP = blood pressure, BUN = blood urea nitrogen, Ca = calcium, CCB = calcium channel blocker, CCIS = modified Charlson Comorbidity Index Score, CKD = chronic kidney disease, Cr = creatinine, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, Hb = hemoglobin, HDL-C = high-density lipoprotein cholesterol, HT = hypertension iPTH, intact parathyroid hormone, LDL-C = low-density lipoprotein cholesterol, No. = number, P = phosphorus, SBP = systolic blood pressure, TG = triglyceride, Total-C = total cholesterol, UPCR = random urine protein/creatinine ratio.
*Significant with normal BP; †Significant with sustained HT; ‡Significant with white-coat HT; §Significant with masked HT.

spectively (11). Among Chronic Renal Insufficiency Cohort (CRIC) Study participants, 67.1% and 46.1% showed clinic BP control rates of < 140/90 and < 130/80 mmHg, respectively (8). However, at Spanish ABPM Registry report showed that only 21.7% and 9.1% of CKD patients maintained clinic BP < 140/90 and < 130/80 mmHg, respectively (7). In Korea, the APrODiTe study reported that 53.4% of CKD patients had controlled clinic BP (< 140/90 mmHg) (10). This study showed a similar controlled clinic BP rate (60.2%).

Previous studies demonstrated that controlled BP rates increased with CKD progression. NKF-KEEP reported that rates of HT awareness, treatment and adequate HT control increased with advancing kidney disease despite increasing prevalence of HT (11). The Spanish ABPM Registry analysis also showed that BP control trends from no CKD to CKD stage 5 increased progressively for BP maintenance at the < 130/80 mmHg threshold. They also reported that 24-hour BP control did not change from no CKD to CKD stage 5 (7). In contrast, Wu et al. (25) reported that 24-hour, daytime, and nighttime SBPs and DPBs were higher in CKD stages 4–5 than CKD stages 1–3. This study demonstrated that clinic SBP was higher in CKD G4 than in other groups. In the case of ABPM, CKD G3b/G4 showed higher 24-hour, daytime, and nighttime SBPs than CKD G1–2/G3a. The ABPM SBPs were not different between CKD G1–2 and CKD G3a or between CKD G3b and CKD G4. Most CKD studies that examined the association between complications and CKD stages were based on the previous 5 stages (26). The recent KDIGO 2012 Guidelines divided stage 3 based on data supporting dif-

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Table 5. Factors related to BP control patterns

Factors	Multivariate OR	95% CI	*P* value
Normal BP			
Age ≥ 61, yr	0.601	0.378–0.957	0.032
Cr (per 1 mg/dL)	0.352	0.237–0.523	< 0.001
HDL-C	1.015	1.002–1.028	0.021
Sustained HT			
Diabetes mellitus	1.921	1.170–3.154	0.010
Ca (per 1 mg/dL)	0.585	0.348–0.980	0.042
LDL-C (per 1 mg/dL)	1.007	1.000–1.014	0.037
White-coat HT			
Age ≥ 61, yr	2.117	1.035–4.331	0.040
Masked HT			
CKD G3b/G4	2.778	1.695–4.552	< 0.001

Normal BP: adjusted for sex, age ≥ 61 years, Diabetes mellitus, CCIS, BUN, Cr, eGFR, CKD G3b/G4, Ca, P, iPTH, UPCR ≥ 1 mg/mg, HDL-C, Hb, albumin, and diuretics; Sustained HT: adujusted for DM, CCIS, Cr, eGFR, Ca, iPTH, UPCR ≥ 1 mg/mg, LDL–C, albumin, and diuretics; White-coat HT: adjusted for age ≥ 61 years, Total-C, and HDL-C; Masked HT: adujusted for CCIS, BUN, Cr, eGFR, CKD G3b/4, and UPCR ≥ 1 mg/mg.
BP = blood pressure, BUN = blood urea nitrogen, Ca = calcium, CCIS = modified Charlson Comorbidity Index Score, CKD = chronic kidney disease, CI = confidence interval, Cr = creatinine, eGFR = estimated glomerular filtration rate, Hb = hemoglobin, HDL-C = high-density lipoprotein cholesterol, HT = hypertension, iPTH = intact parathyroid hormone, LDL-C = low-density lipoprotein cholesterol, OR = odds ratio, P = phosphorus, Total-C = total cholesterol, UPCR = random urine protein/creatinine ratio.

ferent outcomes and risk profiles into categories G3a (eGFR 45–59 mL/min/1.73 mg^2) and G3b (eGFR 45–59 mL/min/1.73 mg^2) (4). This study showed that outcomes and risk profiles as well as BP control patterns, were different between CKD G1–2/G3a and CKD G3b/G4. These results suggest that careful BP monitoring and treatment are essential from the moment CKD patients reach CKD G3b.

Non-/reverse-dipping indicate that nighttime BP did not decrease or was even higher than daytime BP. As non-/reverse-dipping is considered a risk factor of cardiovascular events in non-CKD hypertensive patients, non-/reverse-dipping is considered a risk factor of CKD progression (27,28). Non-/reverse-dipping was also shown to be a risk factor for cardiovascular events and correlated with markers for cardiovascular events in CKD patients (10,14-16,28,29). Multiple factors cause suppressed nighttime BP decrease, such as older age, race, autonomic dysfunction, abnormal sleep-wake cycle, and sodium sensitivity (30). In addition, Feldstein et al. (31) reported that non-dippers were associated with elevated serum Ca in elderly essential hypertensive patients with mild-to-moderate CKD, and Kanbay et al. (32) reported that the non-dipper clinical profile is related to serum Ca, P, and PTH in hypertensive patients with normal renal function. In this study, the nighttime/daytime SBP ratio correlated significantly with the Ca × P product and iPTH. We also suggested that the Ca × P product, iPTH, and albumin were independently associated with non-/reverse-dippers in a multiple logistic regression model even after adjusting for eGFR. In particular, the Ca × P product independently correlated with non-/reverse-dippers after adjusting for nighttime SBP and DBP. Elevated serum P and Ca × P product were associated with poor outcomes according to the International Dialysis Outcomes Practice Patterns Study and a cohort from The Netherlands that included both hemodialysis and peritoneal dialysis patients (33,34). Serum Ca, P, and PTH are factors that promote vascular calcification (35). Increased serum P also stimulates fibroblast growth factor-23 (FGF-23) and PTH secretion. Elevated FGF-23 levels appear to be associated with poor clinical outcomes (35). However, because FGF-23 is not yet routinely measured in general clinical practice, a clinician should estimate CKD-mineral bone disorders using parameters that can be measured easily. The results of this study suggested that abnormal Ca, P, and PTH, all of which reflect abnormal mineral metabolism, vascular calcification, and poor outcome, could predict increased nighttime BP and non-/reverse-dipping.

The high prevalence of white-coat and masked HT in patients with CKD support the need to measure out-of-office BP, such as ABPM or home BP to confirm that a patient's BP is under control. In this study, the prevalence of white-coat and masked HT was 10.1% and 26.9%, respectively. These results were similar to those of the African American Study of Kidney Disease Cohort study (2.2% and 42.9%, respectively), CKD Japan cohort (5.6% and 30.9%, respectively), APrODiTe study (4.3% and 33.9%, respectively), and CRIC Study (4.1% and 27.8%, respectively) (10, 14,18,19). However, the prevalence of white-coat HT and masked HT was respectively 18.3% and 8.3% in meta-analysis by Bangash and Agarwal and 28.8% and 7.0% in the Spanish ABPM Registry, suggesting that their prevalence was respectively ≥ 15% and ≤ 10% (7,17). The differences in the prevalence of BP control type are attributable to race, ethnicity, and renal function in addition to diagnostic thresholds.

Previous studies of CKD cohorts showed that masked HT was associated with low eGFR, elevated urine protein excretion, higher left ventricular hypertrophy and higher pulse wave velocity (10,14,18,19). In this study, masked HT was associated with lower eGFR, higher prevalence of CKD G3b/G4, and elevated UPCR than patients with normal BP. These data indicate that masked HT patients appear to have decreased renal function and elevated proteinuria. Therefore, clinician should carefully monitor out-of-office BP in CKD patients.

This study has several limitations. First, this was a cross-sectional and observational study, and therefore, it has limitations in establishing a cause-effect relationship. Second, important parameters such as FGF-23, echocardiography, and pulse wave velocity, were not obtained; this further limits the clarification of causality. Third, because ABPM was evaluated only once, variability in measurements was not considered. This might result in some degree of misclassification. Finally, because this study had a small number of participants, its statistical power was not high enough for some parameters.

In conclusion, the median ABPM SBPs of CKD G3b and CKD G4 were significantly higher than those of CKD G1–2 and CKD

G3a. ABPM showed a high prevalence of non-/reverse-dippers and sustained/masked HT. Non-/reverse-dippers correlated with higher Ca × P product, higher iPTH, and lower albumin. White-coat HT correlated with old age and sustained HT, with advanced CKD. Clinicians should attempt to perform ABPM in CKD patients, especially in those who are older or have advanced CKD as well as those who have abnormal Ca × P product, iPTH, and albumin.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conceptualization: Oh YK, Oh KH. Data curation: Oh YK, Chin HJ, Ahn SY, An JN, Lee JP, Lim CS, Oh KH. Formal analysis: Oh YK. Writing - original draft: Oh YK.

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