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Association between Central Obesity and Circadian Parameters of Blood Pressure from the Korean Ambulatory Blood Pressure Monitoring Registry: Kor-ABP Registry

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Central obesity has been reported as a risk for atherosclerosis and metabolic syndrome. The influence of central obesity on diurnal blood pressure (BP) has not been established. In this study, we investigated the influence of central obesity on the circadian parameters of BP by 24 hr ambulatory BP monitoring. Total 1,290 subjects were enrolled from the Korean Ambulatory BP registry. Central obesity was defined as having a waist circumference ≥ 90 cm in males and ≥ 85 cm in females. The central-obese group had higher daytime systolic BP (SBP), nighttime SBP and diastolic BP (DBP) than the non-obese group (all, $P < 0.001$). There were no differences in nocturnal dipping (ND) patterns between the groups. Female participants showed a higher BP mean difference (MD) than male participants with concerns of central obesity (daytime SBP MD 5.28 vs 4.27, nighttime SBP MD 6.48 vs 2.72) and wider pulse pressure (PP). Central obesity within the elderly (≥ 65 yr) also showed a higher BP MD than within the younger group (daytime SBP MD 8.23 vs 3.87, daytime DBP 4.10 vs 1.59). In conclusion, central obesity has no influence on nocturnal dipping patterns. However, higher SBP and wider PP are associated with central obesity, which is accentuated in women.

Key Words: Obesity, Abdominal; Blood Pressure Monitoring, Ambulatory; Blood Pressure

INTRODUCTION

Elevation of systolic blood pressure (SBP) is closely related cardiovascular mortality and morbidity (1). Widening of pulse pressure (PP) and loss of normal nocturnal dipping pattern are also considered as important risk factors for cardiovascular mortality with confirming evidence (2, 3). In particular, isolated systolic hypertension (HTN) and widening of PP are factors that are well known to get progressively worse with aging (4, 5).

Obesity, especially, central obesity represents a predominance of visceral fat that exhibit insulin resistance and elevated free fatty acid production related to metabolic syndrome, thrombogenic tendency, inflammation, and increasing risk of coronary heart disease (CHD) (6, 7). Even though it has been well-known that excessive body weight increases the risk of diabetes, CHD, and cholelithiasis in both women and men, the relative risk of diabetes and cardiovascular diseases are approximately one and half or two times higher in women than men (7).

Obesity, which is a modifiable factor unlike aging, has been reported to be associated with increasing blood pressure (BP) in large population and epidemiological studies recently (7-11). Hence, obesity has been regarded as one of the important factors that cause HTN (6). A positive correlation between the degree of weight gaining and the degree of increasing systolic and diastolic BP was shown in both male and female individuals (9). Furthermore, the prevalence of HTN among overweight adults was reported to be 2.9 times higher than that among normal weight adults (11). Some studies have revealed that these effects are more strongly presented in women than men (10), and that these results may show different susceptibilities according to gender. Although a study reported that successful treatment of morbid obesity achieved improvement in nocturnal HTN and dipping patterns (12), the influence of central obesity on diurnal BP has not well been established.

From this point of view, we aimed to investigate the influence of central obesity on circadian patterns and parameters of BP by 24 hr ambulatory blood pressure monitoring (ABPM) with gender and age subgroup analysis.

MATERIALS AND METHODS

The Korean Ambulatory Blood Pressure Monitoring (Kor-ABP) registry

The Kor-ABP registry is a multicenter observational study involving 23 secondary and tertiary hospitals. We selected patients who entered the registry from January 2009 to December

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2010. The Kor-ABP registry enrolled subjects who underwent ABPM from the referral hospital regardless of the goal of the study (the purpose of the ABPM is the following: diagnosis of HTN, 58.3%; examination of the efficacy of antihypertensive therapy, 24.9%; evaluation of hypotensive episode, 1.5%; autonomic dysfunction related, 0.8%; postpartum evaluation of pregnancy induced HTN, 0.4%; checkup before military entrance, 0.3%; and others, 11.9%). We had no specific inclusion or exclusion criteria, but pediatric and pregnant patients were excluded. Medical history of the subjects was collected based on the questionnaire survey and individual medical records.

Ambulatory blood pressure monitoring

Ambulatory BP measurements were recorded using various oscillometric devices such as TM series, A & D Company, Tokyo, Japan in 51%, Tonoport V, GM medical system, Berlin, Germany in 32%, and others in 17%, respectively. ABPMs were performed on working days. The subjects maintained their daily activities and were instructed to keep the arm extended and paused from their activities during inflation of the cuff. The recommended interval for both day and night BP was fixed at 30 min, but variable intervals were permitted according to the referral center preferences. The overall BP measuring frequency was more than every 30 min from 6 a.m. to 10 p.m. in daytime and every 60 min from 10 p.m. to 6 a.m. in nighttime depending on the hospital. Total of 1,729 subjects was enrolled during the period; therefore data from 1,290 subjects were analyzed in this study; 439 subjects were excluded due to incomplete data (25 subjects had lack of ABPM data and 414 subjects had no waist circumference data).

Definition of obesity

Central obesity was defined as a waist circumference (WC) ≥ 90 cm in males, ≥ 85 cm in females, according to the WC cut-off values from the Korean Society for the Study of Obesity (13). WC is obtained by placing a measure in a horizontal plane around the waist at the level of the umbilicus and the superior iliac crests.

Circadian parameters

The averages for daytime and nighttime BP values were calculated for each subject as follows: daytime BP values were calculated using the BP values obtained from 6 a.m. to 10 p.m., nighttime BP values were calculated using the BP values from 10 p.m. to 6 a.m., and nocturnal dipping (ND) was calculated from the following formula (14): (daytime average SBP – nighttime average SBP)/daytime average SBP × 100. Circadian BP patterns were divided into four portions according to ND (14): the riser (ND < 0), the non-dipper (0 ≤ ND < 10), the dipper (10 ≤ ND < 20) and the extreme dipper (ND ≥ 20).

Pulse pressure was calculated by subtracting the mean diastolic BP (DBP) from the mean SBP. PP > 53 was regarded as widened PP (2, 5).

Statistical analysis

Baseline characteristics of subjects were compared using the chi-square test for categorical variables and Student's t-test for continuous variables. Values of continuous variables are expressed as the mean ± standard deviation (SD).

Systolic and diastolic values which appeared to be significant on Student's t-test were entered into the general linear model to adjust for confounding variables (age, given medical history of HTN, diabetes mellitus [DM], dyslipidemia, CHD, heart failure [HF], stroke and sex), interaction of PP and sex, PP and age. Adjusted values of continuous variables are expressed as the adjusted mean ± standard error (SE). To define the relationship between widening of PP and central obesity, the binomial logistic regression model was applied for the calculation of logistic odds ratio and their 95% confidence intervals. A $P < 0.05$ was accepted as statistical significant. Statistical analysis was performed using Statistical Package for the Social Science version 19.0 (SPSS Inc., Chicago, IL, USA).

Ethical statement

This study protocol was reviewed and approved by the institutional review board of Ewha Medical Center (IRB No. ECT 212-24). ABPM data were collected from the patients of referral hospitals after obtaining written informed consents.

RESULTS

Baseline characteristics

The mean age of total 1,290 subjects was 54.2 ± 14.9 yr; the proportion of women was 49.7%. The central-obese group comprised 718 (55.7%) subjects and was older than the non-obese group. There was no difference in female proportion between the two groups. Both groups had similar prevalence of microalbuminuria and HF, smoking, exercise patterns, creatinine, and sleep quality during ABPM. The central-obese group was more likely to have a medical history of stroke, DM, HTN, dyslipidemia, and CHD, and have greater body mass index (BMI) and higher glucose level than the non-obese group (Table 1). The central-obese group had a longer average disease period of HTN (5.90 ± 7.52 yr vs 3.91 ± 6.62 yr) and were taking more than three types of antihypertensive drugs (Table 2, $P = 0.015$).

Systolic and diastolic blood pressure according to age and sex

The central-obese group had higher daytime SBP, nighttime SBP and nighttime DBP than the non-obese group. These results remained after adjusting for covariates: age, HTN, DM, dyslipidemia, CHD, stroke, HF and sex (Table 3). However, there were no significant differences in heart rate and the degree of ND of

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Table 1. Baseline characteristics

Characteristics	Total n = 1,290	Central-obese n = 718 (55.7)	Non-obese n = 572 (44.3)	*P* value
Waist circumference (cm)	88.96 ± 10.33	96.07 ± 6.72	80.03 ± 6.38	< 0.001
Age (yr)	54.24 ± 14.92	57.41 ± 14.44	51.21 ± 15.32	< 0.001
Female (%)	641 (49.7)	367 (51.1)	274 (47.9)	0.263
BMI (kg/m^2)	24.74 ± 3.50	26.26 ± 3.33	22.68 ± 2.62	< 0.001
Microalbuminuria (%)	140 (19.6)	79 (18.7)	61(20.9)	0.503
Cr ≥ 1.3 (mg/dL), (%)	69 (6.3)	43 (6.8)	26 (5.6)	0.451
Glucose (mg/dL)	107.20 ± 33.42	110.13 ± 35.12	102.71 ± 29.05	0.001
Medical history, No. (%)				
DM	164 (12.9)	116 (16.5)	48 (8.5)	< 0.001
HTN	659 (52.1)	401 (57.0)	258 (46.0)	< 0.001
Stroke	134 (10.6)	92 (13.1)	42 (7.5)	0.001
Dyslipidemia	171 (13.6)	118 (17.0)	53 (9.4)	< 0.001
CHD	116 (9.2)	80 (11.4)	36 (6.5)	0.003
HF	22 (1.7)	17 (2.4)	5 (0.9)	0.050
Other factors, No. (%)				
Smoking	471 (36.7)	266 (37.3)	205 (36.0)	0.641
Exercise	673 (53.0)	384 (54.0)	289 (51.6)	0.397
Well-sleep	680 (55.2)	384 (56.6)	296 (53.5)	0.300

Values are presented as mean ± standard deviation. DM, Diabetes mellitus; HTN, Hypertension; BMI, body mass index; CHD, coronary heart disease; HF, heart failure; Cr, creatinine.

Table 2. Antihypertensive medication usage in patients with a history of hypertension

Medication history	Total n = 659 (52.1)	Central-obese n = 401 (57.0)	Non-obese n = 258 (46.0)	*P* value
Duration of HTN (yr)	5.05 ± 7.21	5.90 ± 7.52	3.91 ± 6.62	0.002
Without taking antihypertensive drugs	217 (43.1)	106 (35.9)	111 (53.1)	< 0.01
With antihypertensive drugs, No. (%)				
ARB	181 (34.0)	124 (39.1)	57 (26.5)	0.003
ACEI	40 (7.8)	22 (7.2)	18 (8.5)	0.617
CCB	197 (37.2)	137 (34.4)	60 (28.0)	< 0.001
BB	155 (29.5)	99 (31.8)	56 (26.0)	0.173
Diuretics	113 (21.6)	91 (29.2)	22 (10.4)	< 0.001
Multiple antihypertensive drugs (≥ 3), No. (%)	106 (21.0)	73 (24.7)	33 (15.8)	0.015
Other medication, No. (%)				
Statin	153 (23.2)	100 (24.9)	53 (20.5)	0.074
Aspirin	148 (22.5)	97 (24.2)	51 (19.8)	0.058

Values are presented as mean ± standard deviation. HTN, Hypertension; ARB, angiotensin receptor blocker; ACEI, angiotensin converting enzyme inhibitor; CCB, calcium channel block; BB, beta-blocker.

Table 3. Circadian variables

Blood pressure (mmHg)	Non-obese	Central-obese	Mean difference (95% CI)	Adjusted *P* value*
Day time				
SBP	133.33 ± 15.97	137.93 ± 16.10	-4.80 (-6.67~-2.93)	< 0.001
DBP	84.10 ± 11.17	84.80 ± 10.87	-1.95 (-3.19~-0.70)	0.002
HR	73.64 ± 9.49	73.61 ± 9.64	-1.04 (-2.13~0.04)	0.059
Night time				
SBP	123.30 ± 16.85	127.95 ± 18.37	-4.47 (-6.52~-2.42)	< 0.001
DBP	76.84 ± 11.92	78.21 ± 11.83	-2.10 (-3.48~-0.73)	0.003
HR	64.24 ± 9.77	64.66 ± 9.71	-0.70 (-1.84~0.43)	0.223
ND (%)	7.32 ± 8.64	7.17 ± 8.62	-0.15 (-1.15~0.85)	0.769

ND (%), nocturnal dipping. *Adjusted by age, HTN, DM, dyslipidemia, CHD, stroke, HF and sex. Values are presented as mean ± standard deviation. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

day and night between two groups (Table 3). In the analysis of distinction by sex, female subjects showed a greater BP difference than male subjects in the central-obese group; males only represented significant daytime BP MD related to central obesity (daytime SBP MD 4.27 mmHg; $P = 0.01$, daytime DBP MD 2.28 mmHg; $P = 0.015$), whereas females had difference both in daytime BP and nighttime BP, especially showed greater MD in nighttime SBP related to central obesity (MD 6.48 mmHg, $P <$

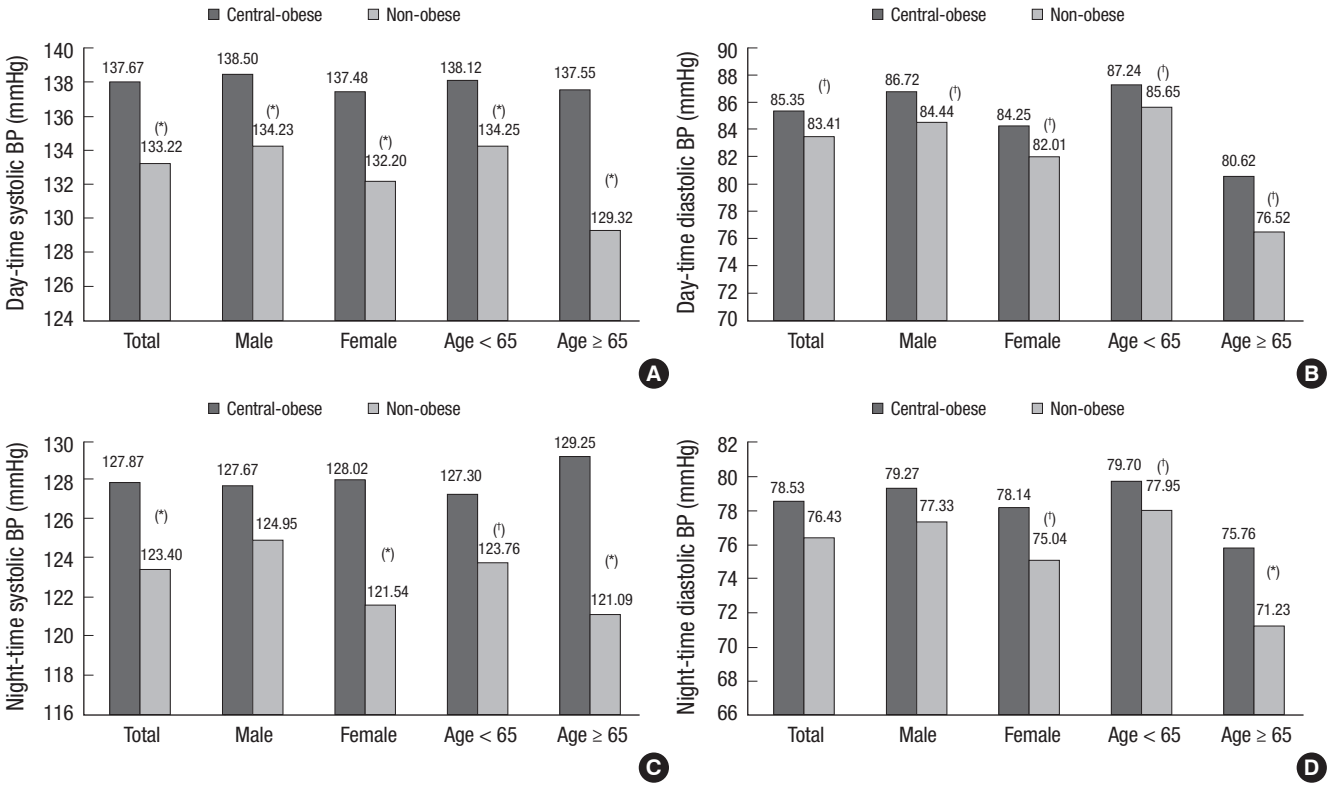

Fig. 1. Day and nighttime blood pressure by sub-groups. (**A**) Daytime systolic BP difference. (**B**) Daytime diastolic BP difference. (**C**) Nighttime systolic BP difference. (**D**) Nighttime diastolic BP difference. *$P < 0.01$, †$P < 0.05$. All values were adjusted by age, HTN, DM, dyslipidemia, CHD, stroke, HF and sex. BP, blood pressure; HTN, hypertension; DM, Diabetes mellitus; CHD, coronary heart disease; HF, heart failure.

Table 4. Pulse pressure by day and night time

Groups by time	Pulse pressure (mmHg)	Adjusted daytime	SE	Adjusted *P* value
Day time				
Central-obese n = 674	53.13 ± 11.78	52.66	0.43	< 0.001
Non-obese n = 540	49.23 ± 10.57	49.81	0.48	
Night time				
Central-obese n = 673	49.73 ± 11.65	49.32	0.41	< 0.001
Non-obese n = 540	46.46 ± 9.90	46.97	0.46	

Values are presented as mean ± standard deviation. Adjusted by age, HTN, DM, dyslipidemia, CHD, stroke, HF, and sex. SE, standard error.

0.001, Fig. 1C). In the analysis of distinction by age, both age groups had higher day and nighttime SBP related to central obesity. These differences were increased in the older group (≥ 65 yr). These results were maintained after adjusting for covariates.

Pulse pressure according to age and sex

The central-obese group showed a wider PP than the non-obese group; daytime and nighttime PP were significantly wider in the central-obese group (daytime PP MD 3.9 mmHg; $P < 0.001$, nighttime PP MD 3.27 mmHg; $P < 0.001$). After adjusting for covariates, these results remained significant (adjusted mean ± SE; daytime PP MD 2.85 ± 0.65 mmHg, nighttime PP MD 2.36 ± 0.63 mmHg; $P < 0.001$, both; Table 4). In the analysis of distinction by sex, central-obese females showed a greater MD than central-obese males (adjusted mean ± SE; MD 3.04 ± 0.95 mmHg vs 1.98 ± 0.91 mmHg). Central-obese females also showed a wider nighttime PP than non-obese female, but this was not the case for males (adjusted mean ± SE; female; MD 3.56 ± 0.90 mmHg, $P < 0.001$, male; MD 0.77 ± 0.89 mmHg, $P = 0.39$). In the analysis of distinction by age, central obesity was also related with widening day and night PP. In particular, those of age ≥ 65 yr showed the widest PP, with MD 4.13 ± 1.48 mmHg in daytime and 4.02 ± 1.42 mmHg in nighttime (adjusted mean ± SE, Fig. 2). These effects remained after the interaction analysis between central obesity with age (daytime $P = 0.005$, nighttime $P = 0.002$, Fig. 2). PP > 53 was independently related with age, central obesity and stroke (Table 5).

Nocturnal dipping patterns

The distributions of nocturnal dipping patterns were similar between the groups. The most frequent pattern was non-dipper 764 (44.8%), followed by dipper 476 (27.9%), riser 357 (21.0%) and extreme dipper 107 (6.3%). This distribution failed to show

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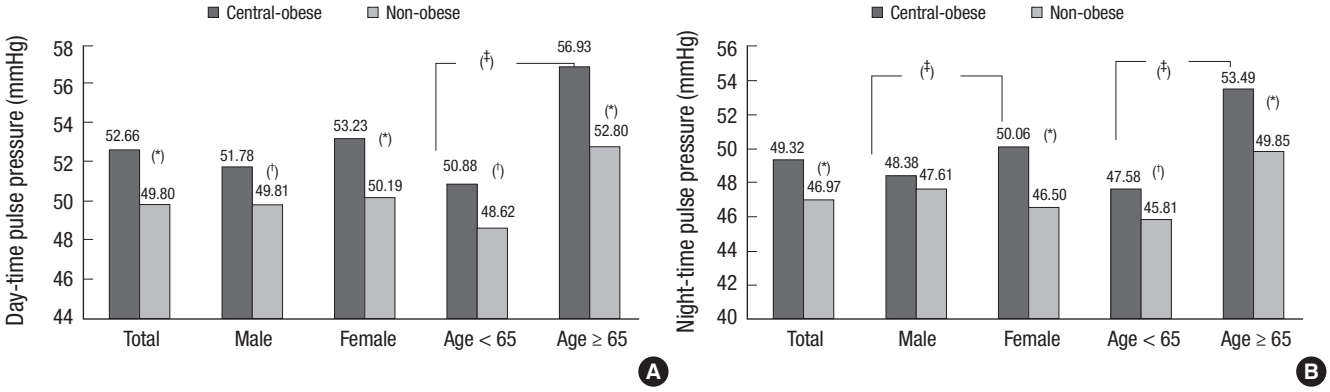

Fig. 2. Day and nighttime pulse pressure according sub-groups. (**A**) Daytime pulse pressure. (**B**) Night time pulse pressure. *$P < 0.01$, †$P < 0.05$, ‡P for interaction < 0.01. All values were adjusted for age, HTN, DM, dyslipidemia, CHD, stroke, HF and sex. HTN, hypertension; DM, Diabetes mellitus; CHD, coronary heart disease; HF, heart failure.

Table 5. Covariables affect pulse pressure by binomial logistic regression

Variables	Daytime PP > 53 mmHg		Nighttime PP > 53 mmHg	
	OR	95% CI	OR	95% CI
Age*	1.014	1.005-1.023	1.024	1.014-1.034
Sex	1.074	0.838-1.377	1.014	0.773-1.331
DM	1.690	1.152-2.477	2.254	0.864-1.502
Dyslipidemia	0.815	0.570-1.166	0.692	0.464-1.031
Central obesity*	1.607	1.251-2.064	1.444	1.093-1.907
Stroke*	2.553	1.723-3.782	2.170	1.461-3.222
CHD	0.788	0.512-1.211	0.719	0.450-1.147
CHF	0.941	0.409-2.63	0.998	0.383-2.605

Daytime PP, daytime pulse pressure; Nighttime PP, nighttime pulse pressure; 95% CI, 95% confidence interval; DM, Diabetes mellitus; CHD, coronary heart disease; CHF, congestive heart failure.

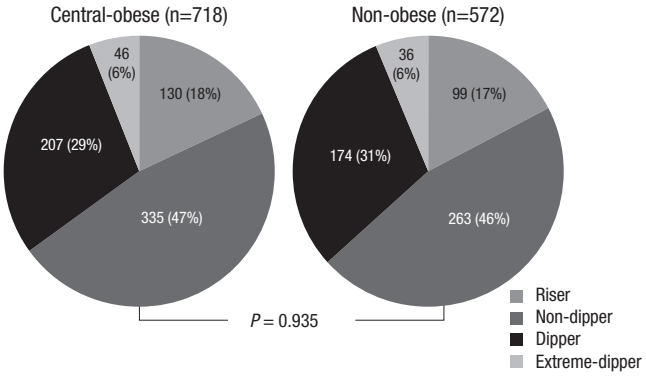

Fig. 3. Nocturnal dipping pattern.

any difference according to central obesity (Fig. 3) and analysis of distinction by sex and age.

DISCUSSION

In the present study, we evaluated the relationship between central obesity and the circadian parameters of BP obtained by ABPM in secondary and tertiary hospitals. Central obesity was related with rising day and night SBP and DBP. These similar levels of rising day and night SBP resulted in no change in nocturnal dipping patterns according to obesity. However, the central-obese group showed a greater increase in SBP than DBP, which resulted in rising PP. Rising PP was more frequently detected in females than males and in those of age ≥ 65 yr than age < 65. In particular, age and obesity showed an independent relationship to widening PP.

It is well known that obesity has a role in increasing SBP; in fact, BMI has a positive correlation with the prevalence of HTN (6, 11). In this study, the central-obese group had a longer average disease period of HTN and was taking more antihypertensive medications. This suggested that the central-obese group had more severe HTN, even though we did not have data about secondary or malignant HTN in the registry we used. Additionally, the central-obese group showed higher day and nighttime systolic and diastolic BP. Mean difference of these parameters was higher in day and night SBP (4.80 mmHg, 4.47 mmHg) than day and night DBP (1.94 mmHg, 2.1 mmHg). These phenomena related with rising PP in central obesity.

The mechanism of increasing BP related obesity has not been fully established. Insulin resistance, renin angiotensin system activation, sympathetic nervous system activation, endothelial dysfunction with oxidative stress, and obstructive sleep apnea are suspected to play a major role in increasing BP (15).

PP reflects stiffness of large arteries which means atherosclerosis (5, 16). Recent studies have shown the positive relationship between obesity and arterial stiffness (17). PP rises with age and has been accepted as a predictor of cardiovascular disease, CHD, HF, and stroke (18, 19). Isolated systolic HTN and rising PP in the elderly are related to adverse cardiovascular outcome (4). A study showed that the average 24-hr PP had a consistent association with left ventricular mass, carotid intima-media thickness after adjusting for covariates (20).

PP is so easily affected by the white coat effect, physical activity related stroke volume, and sympathetic activation that office

PP can often be overestimated. For this reason, ambulatory PP is better than office PP when predicting target organ damage in hypertensive patients (2). Rising PP in the central-obese group was still significant after adjusting for covariates. Concerning gender differences, females showed a tendency towards rising PP than obese males. An interesting finding was that females had a wider night time pulse pressure in relation to obesity, but this was not the case in males. This significance still remained after the interaction analysis of central obesity and sex (P = 0.014). During daytime, individuals could perform various physical activities and stimulate sympathetic activation which may affect stroke volume and PP. However, the night time has less eventful so that has less confounding factors. Thus, this finding may suggest different gender susceptibility about obesity. In fact, central-obese women had a higher relative risk of DM and HF with increasing abdominal circumference than men (7). A population-based cross-sectional study with five-year prospective mortality showed that BMI has an association with diastolic dysfunction which is highly associated with left ventricular mass only in women and in persons < 65 age after stratification for age, gender and HTN (21).

Several studies have reported gender differences about the effect of obesity and change in body weight on BP (9, 10) and cardiovascular outcome (7, 21). From these results, women can be considered to be more susceptible to the cardiovascular adverse effects related to obesity. Accentuated rising of PP in central-obese women may have a role in these cardiovascular vulnerability. However, the answer to the reason for these sex differences is not clear. One pointed out that such gender differences resulted from hormonal changes related to menopause and sudden changes in body weight (10). With regard to gender differences in body fat composition, males who usually have a greater amount of visceral adipose tissue and have less protective effects from estrogen usually show inferiority in cardiovascular risks (22). Similarity, central-obese women have a greater android fat distribution than lean women which related to consequently have insulin resistance (23). Insulin resistance and changes in the autonomic nervous system as a result of redistribution of body fat composition may have an impact on the cardiovascular system in obese women. However, obesity related difference of gender susceptibility to the cardiovascular system needs further investigation.

Our data showed that the prevalence of non-dipper is 46%-47% in both groups. The prevalence of non-dipper is different depending on other factors such as age, BP and cardiovascular risk factors (14). Recent studies have reported the prevalence of non-dippers to be 45.9%; who have no history of diabetes and an average age of 56 yr, and 46.0%; who have no cardiovascular risks and an average age of 54.4 yr, respectively (24, 25). These data are similar in prevalence of non-dippers to our data.

We could not find any association between central obesity and nocturnal dipping patterns in this study. The central-obese group were taking multiple antihypertensive drugs compared to the non-obese group (P = 0.015); however, there was no known evidence about pharmacologically induced switching of dipping status (26, 27). The central-obese group had a higher mean BMI of 26.26 ± 3.3 kg/m^2 than that of the non-obese group, but the subjects were far from morbid obesity. A study presented an improved ND pattern after biatric surgery, and the mean BMI of the subjects was over 40 kg/m^2 (12). Their one year follow up showed improvement in ND pattern and 30% reduction in mean body weight. Hence, if we evaluated the morbid obesity compared to non-obese individuals, there would be some changes in our results. However, the conclusion is opened to future studies.

There were several limitations to this study. We observed, as this was a cross-sectional study, the predictive factors and the outcomes variables simultaneously and had no follow up data. Thus, it was difficult to establish any causal or temporal relationship. Generally, hypertensive patients were managed at primary clinics, but this study was based on data from secondary and tertiary hospitals. Our ABPM data was obtained using various oscillometric devices from different institutes. All participants were Korean, and we had limitation to generalize our results to populations of other ethnic groups.

In conclusion, central obesity has no influence on nocturnal dipping patterns. However, higher SBP and wider PP are associated with central obesity, which is accentuated in women.

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DISCLOSURE

All authors have no conflicts of interest relevant to this article to disclose.

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