Original Article

Regular Alcohol Drinking Is a Determinant of Masked Morning Hypertension Detected by Home Blood Pressure Monitoring in Medicated Hypertensive Patients with Well-Controlled Clinic Blood Pressure: The Jichi Morning Hypertension Research (J-MORE) Study

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Morning blood pressure (BP) level may play an important role in the pathogenesis of cardiovascular events; however, morning BP detected by home BP monitoring may remain uncontrolled in medicated hypertensive patients even when clinic BP is well controlled (masked morning hypertension: MMHT). We studied the determinants of MMHT in stably medicated hypertensive outpatients. In the Jichi Morning Hypertension Research (J-MORE) study, 969 consecutive hypertensive outpatients were recruited by 43 doctors in 32 different institutes. They had been under stable antihypertensive medication status at least for 3 months. Clinic BP was measured on 2 different days and self-measured BP monitoring was conducted twice consecutively in the morning and evening for 3 days. Four-hundred and five patients had well-controlled clinic BP (systolic BP [SBP]<140 mmHg and diastolic BP [DBP]<90 mmHg). Among them, 246 patients (60.7%) had MMHT (morning SBP≥135 mmHg and/or DBP≥85 mmHg). Compared with the patients with normal clinic BP and morning BP, the patients with MMHT had a significantly higher prevalence of regular alcohol drinkers (35.0% *vs.* 23.3%, $p=0.012$), a significantly higher number of antihypertensive drug classes (1.83±0.82 *vs.* 1.66±0.84, $p=0.04$) and a significantly higher clinic BP level (SBP: 130.4±7.6 mmHg *vs.* 127.8±8.4 mmHg, $p=0.001$; DBP: 75.5±7.6 mmHg *vs.* 73.6±7.6 mmHg, $p=0.013$). In logistic regression analysis, independent determinants for MMHT were regular alcohol drinking (odds ratio [OR]: 1.76; 95% confidence interval [CI]: 0.99–3.12; $p=0.05$) and higher-normal clinic BP (130/85 mmHg<clinic SBP/DBP<140/90 mmHg) (OR: 1.60; 95% CI: 1.05–2.44; $p=0.03$) after adjustment for confounding factors. The patients who both drank alcohol regularly and had a higher-normal clinic BP had 2.71 times higher risk for MMHT than those who did not drink alcohol regularly and had a relatively lower-normal clinic BP (<130/85 mmHg) ($p<0.01$). In conclusion, regular alcohol drinking is an independent determinant for MMHT detected by home BP monitoring in medicated hypertensive patients with well-controlled clinic BP. (*Hypertens Res* 2006; 29: 679–686)

***Key Words*: masked hypertension, morning hypertension, alcohol, home blood pressure**

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Introduction

Cardiovascular events tend to occur in the morning (*1*). Morning blood pressure (BP) levels may play an important role in the pathogenesis of target organ damage (*2–4*), cognitive dysfunction (*5*), and cardiovascular events (*6*, *7*). However, morning BP remains uncontrolled even in some medicated hypertensives with well-controlled clinic BP (*8*) (masked morning hypertension: MMHT).

Pickering *et al*. (*9*) called the state of elevated ambulatory BP despite well-controlled clinic BP "masked hypertension," and a number of studies have shown that the level of risk of cardiovascular events and target organ damage is increased under this condition (*10*, *11*). Ambulatory BP monitoring has a better prognostic value than clinic BP measurements (*12*), and the definition of masked hypertension was derived from a comparison between ambulatory BP monitoring and clinic BP measurements.

Recently, self-measured BP monitoring has become widely available. Masked hypertension evaluated by self-BP monitoring at home was also reported to be a risk factor for cardiovascular events in medicated hypertensive patients (*13*). Most of the reported data of home BP monitoring have been the average of morning and evening BP levels according to the guidelines (*14–16*) for the management and treatment of hypertension. However, Ohkubo *et al*. (*6*) reported that home BP measurement in the morning was a better predictor of mortality than clinic BP in the general population. The guidelines of the Japanese Society of Hypertension (*17*) recommend home BP measurement in the morning. Morning BP tends to be higher than evening BP, and we may underestimate the presence of uncontrolled hypertension at home if we use the average of morning and evening BP levels. In addition, morning BP is a pitfall of current antihypertensive medication (*8*). Therefore, we evaluated determinants of MMHT detected by home BP monitoring in medicated hypertensive patients with well-controlled clinic BP, who were participants in the Jichi Morning Hypertension Research (J-MORE) study (*18*).

Methods

Patients

One thousand and twenty-seven hypertensive outpatients who had stable antihypertensive drug treatment status for at least 3 months were recruited by 43 doctors from 32 different clinics and hospitals in Japan.

Patients who reported, in the physician's interview, that they drank alcohol every day were considered regular alcohol drinkers. Smoking was defined as having a current smoking habit. Chronic renal disease was defined as overt proteinuria and/or an elevated serum creatinine level of more than 176.8 μmol/l (2.0 mg/dl). Diabetes mellitus was defined as a fasting blood glucose level of more than 7.0 mmol/l (126 mg/dl) or a casual glucose level of more than 11.1 mmol/l (200 mg/dl) in patients who were not being treated or a self-reported diagnosis of diabetes mellitus. Glucose intolerance was defined as a fasting blood glucose level in the range of 6.1–6.9 mmol/l (110–125 mg/dl). Hyperlipidemia was defined as a total cholesterol level higher than 5.7 mmol/l (220 mg/dl) or triglyceride level higher than 1.7 mmol/l (150 mg/dl). Past histories of the patients were obtained by interviews by the patients' own doctors.

The antihypertensive medications were classified as calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β-blockers, diuretics, α-blockers or others. Patients who were taking verapamil or diltiazem and a dihydropyridine CCB were classified as taking one CCB. αβ-Blocker was classified as taking β-blocker.

The institutional review board of Jichi Medical University approved this study, and informed consent was obtained from all patients.

Study Protocol

All of the patients were instructed to measure morning and evening BP using commercially available self-measurement BP devices for which the accuracy was validated. They were instructed to measure BP using a cuff-oscillometric device at the same upper arm position for 3 days (*19*). Patients who were not already using their own self-measurement BP devices in daily practice were given cuff-oscillometric semi-automatic devices (UA-631; A&D, Tokyo, Japan) (*20*) for use in this study. Self-measured BP monitoring was performed twice on each occasion on a bare arm with the patient in a seated and relaxed position in the morning (within 1 h after waking, before having breakfast and taking medication) and evening (just before going to bed) for 3 consecutive days (6 points). The first measurement was performed after more than 2 min of rest and the second measurement was performed after an interval of more than 30 s. The patients were asked to document all of the self-measured BP values on a sheet of paper and report them to their own physicians.

Morning BP and evening BP were defined as the average of the first and the second self-measured BP values in the morning and in the evening, respectively, for 3 days (total 6 BP measurements). Clinic BP was measured after resting for at least 5 min at 2 different clinic visits before and after the self-measured BP monitoring period. Clinic BP was measured by physicians or nurses using validated BP measurement devices that they usually used to measure BP in their daily practice. Clinic BP was measured between 9 AM and 5 PM, and was not measured at the trough time. Clinic BP was defined as the average of the BPs measured at the 2 visits.

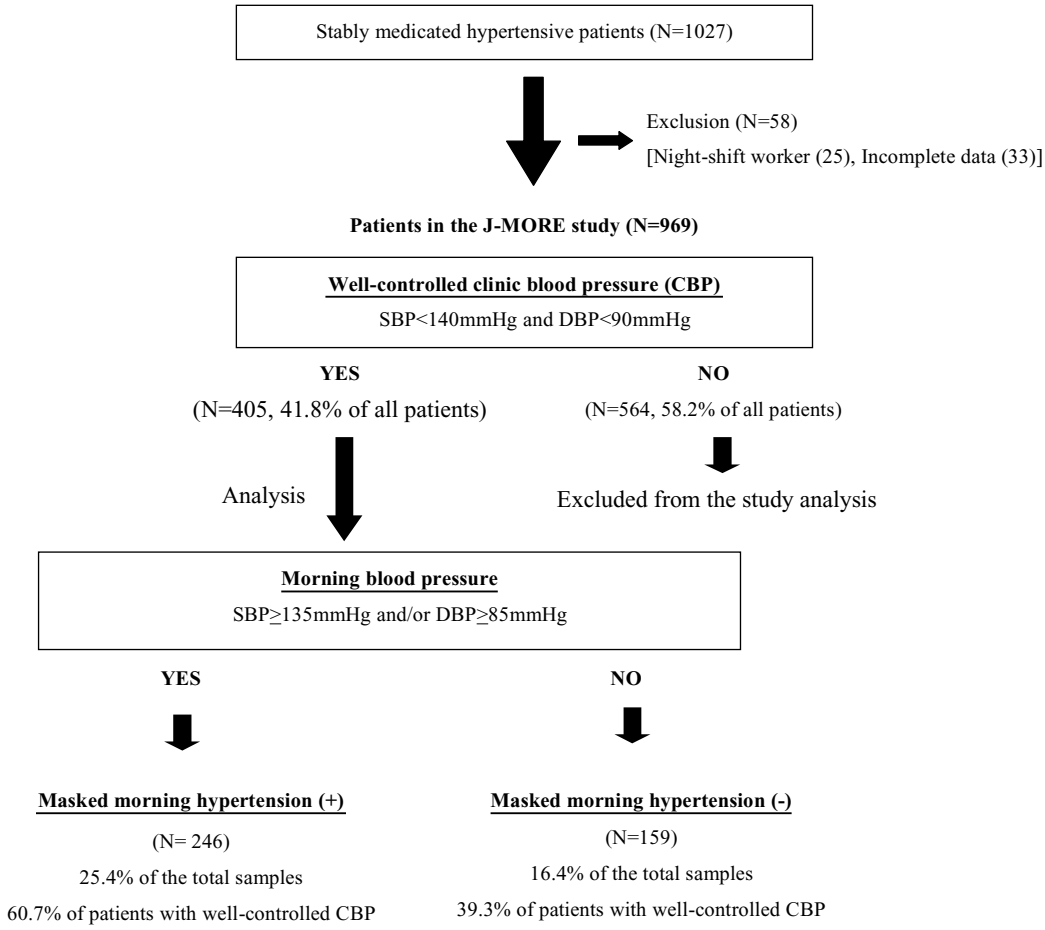

Fig. 1. *The prevalence of masked morning hypertension in medicated hypertensive patients.*

Statistical Methods

After excluding 58 patients who were night-shift workers (25 patients) or who had incomplete data sets (33 patients), statistical analyses were finally conducted for 969 patients using computer software SPSS version 11.0J (SPSS Inc., Chicago, USA). Comparisons of two parameters were performed by the two-tailed non-paired *t*-test and comparisons of categorical variables were performed by the χ^2 test. The odds ratio (OR) and the 95% confidence interval (CI) were calculated by logistic regression analysis. A probability value <0.05 was considered statistically significant.

Results

Prevalence of MMHT

Four-hundred and five patients had well-controlled clinic BP (systolic BP [SBP]<140 mmHg and diastolic BP [DBP]<90 mmHg). Among them, 246 patients (60.7% of patients with well-controlled clinic BP and 25.4% of all patients) had MMHT (morning SBP≥135 mmHg and/or DBP≥85 mmHg), and 159 patients did not have MMHT (Fig. 1).

There were 149 patients with evening hypertension (evening SBP≥135 mmHg and/or evening DBP≥85 mmHg) among the patients with well-controlled clinic BP. The number of patients who had uncontrolled BP only in the morning was 116 (28.6%), while the number who had uncontrolled BP only in the evening was 19 (4.7%), and the number who had uncontrolled BP in both the morning and evening was 130 (32.1%).

MMHT (+) *vs.* MMHT (–)

There was a significantly higher prevalence of regular alcohol drinkers (35.0% *vs*. 23.3%, $p=0.012$), number of antihypertensive drug classes (1.83±0.82 *vs*. 1.66±0.84, $p=0.04$), percentage of patients using all types of CCBs (79.7% *vs*. 67.9%, $p=0.008$), percentage of patients using long-acting CCBs (67.9% *vs*. 56.0%, $p=0.015$), and percentage of patients taking antihypertensive medication at night (43.9% *vs*. 26.4%, $p<0.001$) among patients with MMHT than among those without MMHT (Table 1).

On the other hand, there were no significant differences in

Table 1. Characteristics of the Patients with Masked Morning Hypertension and Normotension among Patients with Well-Controlled Clinic BP

	MMHT (–) (n=159)	MMHT (+) (n=246)	p
Age (years)	66.6±9.6	67.1±9.8	0.60
Male (%)	41.5	48.0	0.20
Body mass index (kg/m^2)	23.6±3.5	24.1±3.5	0.13
Smokers (%)	11.9	13.8	0.59
Regular alcohol drinkers (%)	23.3	35.0	0.012
Hyperlipidemia (%)	35.2	41.1	0.24
Diabetes or impaired glucose tolerance (%)	13.8	12.2	0.63
Chronic renal dysfunction (%)	3.8	4.1	0.88
Number of antihypertensive drug classes	1.66±0.84	1.83±0.82	0.04
Calcium channel blockers (%)	67.9	79.7	0.008
Short–intermediate acting (%)	12.6	14.2	0.64
Long-acting (%)	56.0	67.9	0.015
β-Blockers (%)	18.2	26.0	0.069
ACE inhibitors (%)	25.8	22.8	0.49
ARBs (%)	30.8	29.7	0.81
α-Blockers (%)	11.3	15.4	0.24
Diuretics (%)	11.3	9.8	0.61
Nitrates (%)	0.0	2.0	0.070
Clinic SBP (mmHg)	127.8±8.4	130.4±7.6	0.001
Clinic DBP (mmHg)	73.6±7.6	75.5±7.6	0.013
Patients with clinic BP≥130/80mmHg (%)	35.3	64.7	<0.05
Clinic PR (/min)	71.9±9.4	71.3±9.6	0.58
Morning SBP (mmHg)	125.0±7.2	144.1±10.6	<0.001
Morning DBP (mmHg)	74.4±6.8	84.1±8.9	<0.001
Morning PR (/min)	64.5±8.6	65.2±9.6	0.51
Evening SBP (mmHg)	121.6±10.9	132.9±12.0	<0.001
Evening DBP (mmHg)	71.1±7.7	76.8±9.5	<0.001
Evening PR (/min)	68.4±8.4	68.4±9.1	0.45

Data were shown as mean±SD or percentage. BP, blood pressure; MMHT, masked morning hypertension; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate. Overall p values were calculated by non-paired t-test or χ^2 test.

the parameters listed above between patients with masked evening hypertension (clinic BP<140/90 mmHg and evening BP≥135/85 mmHg) and patients without masked evening hypertension (data not shown).

Regular Alcohol Drinkers

There were 123 regular alcohol drinkers (30.4%) among the patients with well-controlled clinic BP. In the regular alcohol drinkers, morning SBP (138.5±13.2 *vs*. 135.8±13.2 mmHg, p=0.07), morning DBP (82.0±9.1 *vs*. 79.6±9.5 mmHg, p=0.02), percentage of males (86.6% *vs*. 26.6%, p<0.001) percentage of smokers (32.5% *vs*. 4.0%, p<0.001), number of antihypertensive drug classes used (1.9±0.8 *vs*. 1.7±0.8, p=0.04), and percentage of renal dysfunction (7.3% *vs*. 2.5%, p=0.02) were higher than those in the non-drinkers, but clinic BPs, evening BPs, percentage of hyperlipidemia, percentage of diabetes or impaired glucose tolerance, and antihypertensive drugs used did not show significant differences.

Determinants of MMHT

In the logistic regression analysis, regular alcohol drinking was an independent risk factor for MMHT (OR: 1.63; 95% CI: 1.03–2.58; p=0.038) after adjustment for significant covariates such as number of antihypertensive drug classes used, clinic SBP, and clinic DBP. Even after we added long-acting CCB use and the percentage of patients who were taking antihypertensive medication at night into the model, regular alcohol drinking had a tendency to be a risk factor for MMHT (OR: 1.59; 95% CI: 0.99–2.53; p=0.054).

Additionally, regular alcohol drinking was a significant determinant for MMHT (OR: 1.84; 95% CI: 1.04–3.25; p=0.036) after adjustment for confounding factors such as

Table 2. Determinants of Masked Morning Hypertension among the Patients with Well-Controlled Clinic BP

	Model 1			Model 2		
	OR	95% CI	*p*	OR	95% CI	*p*
Age (10 years)	1.11	0.90–1.78	0.34	1.12	0.90–1.40	0.29
Sex (male *vs*. female)	0.96	0.58–1.59	0.87	0.92	0.55–1.53	0.74
BMI (kg/m^2)	1.03	0.97–1.09	0.37	1.02	0.96–1.09	0.45
Smokers (no=0, yes=1)	0.88	0.45–1.73	0.71	0.90	0.46–1.78	0.77
Drinkers (no=0, yes=1)	1.84	1.04–3.25	0.036	1.76	0.99–3.12	0.05
Hyperlipidemia (no=0, yes=1)	1.36	0.88–2.10	0.17	1.29	0.83–2.00	0.25
DM or IGT (no=0, yes=1)	0.81	0.44–1.49	0.49	0.83	0.45–1.55	0.57
Antihypertensive drug classes	1.21	0.94–1.57	0.15	1.23	0.95–1.59	0.15
Clinic BP≥130/85 mmHg, *vs*. <130/85 mmHg				1.60	1.05–2.44	0.03

DM, diabetes mellitus; IGT, impaired glucose tolerance; BP, blood pressure; OR, odds ratio; 95% CI, 95% confidence interval. OR, 95% CI, and *p* values were calculated by logistic regression analysis.

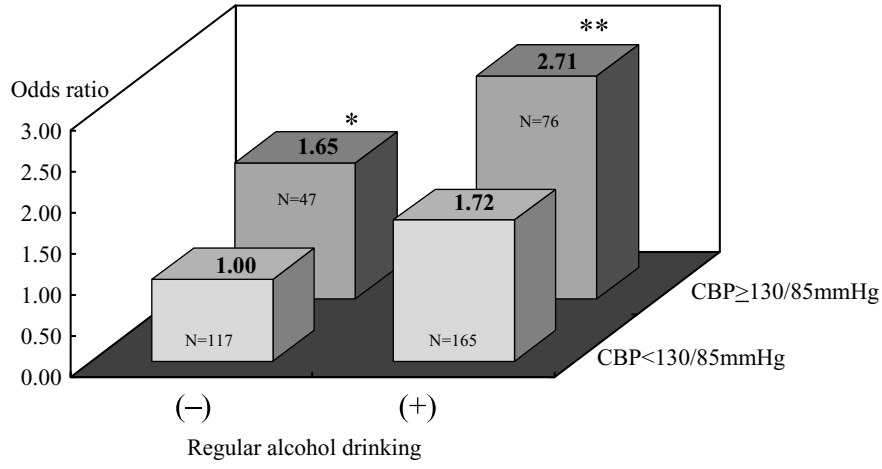

Fig. 2. *The odds ratio of masked morning hypertension in the patients who were regular alcohol drinkers and had clinic BP≥130/85 mmHg. CBP, clinic blood pressure. Adjusted for age, sex, BMI, smoking, number of antihypertensive drug classes, and calcium channel blocker use by logistic regression analysis. Odds ratio:* vs*. regular alcohol drinking (–) and CBP<130/85 mmHg group,* *p*<0.05, **p*<0.01.*

age, sex, smoking, presence of hyperlipidemia, presence of diabetes or impaired glucose tolerance, and number of antihypertensive drug classes used (Table 2). Even after the patients with higher-normal clinic BP (130/85 mmHg≤clinic BP<140/90 mmHg) were added to the model, regular alcohol drinking and the percentage of patients with higher-normal clinic BP were determinants for MMHT (Table 2). The patients who both drank alcohol regularly and had relatively higher-normal clinic BP had 2.71 times higher risk of MMHT (p<0.01), compared with those who did not drink alcohol regularly and had relatively lower-normal clinic BP (clinic BP<130/85 mmHg) (Fig. 2).

Discussion

Regular alcohol drinking and higher-normal clinic BP were independent determinants of MMHT in the present study. This result shows the importance of home BP monitoring in patients who drink alcohol regularly to detect MMHT and achieve 24-h BP control.

Medicated hypertensive patients who drink alcohol regularly and had relatively higher-normal clinic BP (130/85≤clinic BP<140/90 mmHg) had increased risk of MMHT as evaluated by home BP monitoring. There is little reported data about the determinants of masked hypertension. Liu *et al*. (*11*) reported that their group of subjects with hypertension (based on ambulatory BP monitoring) had higher age, body mass indices, serum creatinine concentrations, and glucose levels, and a higher prevalence of smokers than their group of subjects with normotension. Additionally, Lurbe *et al*. (*21*) reported that their young subjects with masked hypertension had higher ambulatory pulse rate, were more obese,

and were 2.5-times more likely to have a parental history of hypertension than their young subjects without masked hypertension. These determinants of masked hypertension were correlated with known risk factors for cardiovascular disease; however, they were derived from data of untreated subjects.

In the Self-Measurement of Blood Pressure at Home in the Elderly: Assessment and Follow-Up (SHEAF) study, Bobrie *et al*. (*13*) found that masked hypertension detected by home BP monitoring was associated with an increased risk for cardiovascular events even among treated patients. In the SHEAF study, the home BP value was defined as the average of the morning BP and evening BP levels; however, an elevation of the morning BP level might have contributed to the increase of cardiovascular risk (*2*, *3*, *6*, *22*). Therefore, it was important to evaluate the determinants of MMHT detected by home BP monitoring among well-controlled medicated hypertensive patients. Additionally, we could not find a significant determinant of uncontrolled evening BP in the present study.

Most of the reported data regarding masked hypertension have been derived from ambulatory BP monitoring. Home BP is measured in a seated position after taking a rest. In contrast, ambulatory BP includes daytime BP variability due to physical activity and nighttime BP changes, and findings made using ambulatory BP and home BP are not always identical. Ambulatory BP monitoring is reported to have better prognostic value than home BP monitoring (*23*). However, it is difficult to perform ambulatory BP monitoring in all hypertensive patients (*24*), and home BP monitoring is an easier screening method to detect uncontrolled BP in the daytime (*25*). Therefore, the results of the present study showed that we should pay attention to alcohol drinkers when we evaluate morning BP by home BP monitoring.

Kawano *et al*. (*26*) reported that alcohol drinking immediately reduces evening BP level and gradually increases morning BP level in home BP monitoring, and that effects on sodium retention were one of the causes of the BP change during the period of alcohol drinking (*27*). However, the mechanisms of the hypertensive effect due to alcohol drinking have not been clarified, although possible mechanisms are reported to include effects on neurohumoral substances, vascular smooth muscles and the endothelium (*27*). Kurihara *et al*. (*28*) reported that excessive alcohol intake increases the risk of arterial stiffening in men with normal BP. In the present study, the regular alcohol drinkers used a higher number of antihypertensive drug classes, reflecting the difficulty of controlling their BP. Even after clinic BP was well controlled with the additional antihypertensive drugs, morning BP remained uncontrolled.

In the J-MORE study, we found previously that regular alcohol drinking, age, male sex and β-blocker use were the determinants for an exaggerated difference of morning SBP minus evening SBP level (ME difference) (*18*). An increased ME difference partly increases the risk for MMHT; however, in the present study, there were also patients with uncontrolled BP both in the morning and evening. Usually, people drink alcohol with dinner, and alcohol has acute effects on BP. Evening BP is decreased just after alcohol drinking and clinic BP is the BP during the alcohol-free period. On the other hand, repeated alcohol drinking is reported to have chronic effects on sodium balance and BP, increasing BP in both the morning and evening without changing the ME difference (*27*). These acute and chronic effects of alcohol on home BP may explain why regular alcohol drinking was a risk for factor both MMHT and ME difference.

There was a tendency for regular alcohol drinkers to have increased risk for MMHT independently of clinic BP level, although the risk of MMHT was higher in the patients with higher-normal clinic BP than in those who drank alcohol regularly. Moreover, the patients who had relatively higher-normal clinic BP (130/85 mmHg≤clinic BP<140/90 mmHg) and drank alcohol regularly had 2.71-times higher risk of MMHT. Liszka *et al*. (*29*) reported that even participants with prehypertension (130/85 mmHg≤clinic BP<140/90 mmHg) had 1.42 times higher risk of cardiovascular mortality in the National Health and Nutrition Examination Survey I (1971–1975). The patients with higher-normal clinic BP level might have had an increased risk of cardiovascular mortality in association with MMHT. Regular alcohol drinking might increase the level of risk of MMHT in patients with higher-normal clinic BP.

MMHT in medicated hypertensive patients means that there are uncontrolled BPs during the day. Morning BP level includes the trough effect of antihypertensive medications when patients are taking antihypertensive medication in the morning (*30*). In the present study, the patients with MMHT were more likely to take antihypertensive drugs and long-acting CCBs, and more likely to take antihypertensive medication at night. Long-acting antihypertensive drugs seem to be beneficial for controlling morning BP level when the patients are taking antihypertensive drugs in the morning. A number of types of CCBs were used in the present study, and 79.6% of the patients with MMHT were taking CCBs. It is not known why there was a higher percentage of CCB use in the patients with MMHT. Probably, the physicians tried controlling morning BP by using long-acting CCBs or prescribing antihypertensive drugs at night; however, regular alcohol drinking had a tendency to be an independent determinant of MMHT even after adjusting for these confounding factors, and this may show the difficulty of controlling BP in the morning. Additionally, a higher percentage of the patients with MMHT took antihypertensive medication at night. The fact that patients tend to show worse adherence to regimens in which a drug is taken at bedtime than to those in which a drug is taken in the morning might have played a role in the increase of MMHT, especially in regular alcohol drinkers.

Study Limitations

In the present study, we did not take information about the amount of alcohol intake in regular drinkers. This is important to evaluate the relationship between alcohol and hypertension and a limitation of the present study.

Ambulatory BP has a better prognostic significance than home BP (*23*), and differences of the findings regarding masked hypertension as detected by ambulatory BP *vs*. that detected by home BP are not uncommon (*25*). In the clinical setting, it is difficult to perform ambulatory BP in all patients. We used only home BP to detect MMHT which is reported to be an appropriate method for detecting this condition (*25*).

Conclusion

Regular alcohol drinking is a risk factor for MMHT in medicated hypertensive patients with well-controlled clinic BP. Home BP monitoring and evaluation of morning BP are mandatory in regular alcohol drinkers, even if the patients have well-controlled clinic BP.

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