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ORIGINAL ARTICLE

Relationship of dysregulation of glucose metabolism with white-coat hypertension: the Ohasama study

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Characteristics of glucose metabolism in subjects with white-coat hypertension (WCHT) have not been fully investigated. The purpose of this study was to determine the relationship between glucose metabolism and WCHT on the basis of blood pressure (BP) at home (HBP) in the general population. Participants were from Ohasama, a rural Japanese community, and included 466 residents (mean age, 61.0 years) who had no history of diabetes mellitus. HBP and oral glucose tolerance test values were measured. Participants were classified into four groups on the basis of their HBP and casual-screening BP (CBP) values: normotension (NT) (HBP < 135/85 mm Hg, CBP < 140/90 mm Hg); WCHT (HBP < 135/85 mm Hg, CBP ⩾ 140/90 mm Hg); masked hypertension (HBP ⩾ 135/85 mm Hg, CBP < 140/90 mm Hg); or sustained hypertension (SHT) (HBP ⩾ 135/85 mm Hg, CBP ⩾ 140/90 mm Hg). The relationships between glucose metabolism and BP among the four groups were examined using multivariate analysis adjusted for possible confounding factors. Factors in relation to glucose metabolism, such as fasting glucose level, 2-h postchallenge glucose level and homeostasis model assessment-insulin resistance index, were significantly higher in subjects with WCHT and SHT than in those with NT (all $P < 0.03$). When men and women were analyzed separately, these relationships were more pronounced in women. Our results suggest that dysregulation of glucose metabolism in WCHT might contribute to the increase in the long-term cardiovascular risk among the general population.
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Keywords: general population; glucose metabolism; home blood pressure; oral glucose tolerance test; white-coat hypertension

INTRODUCTION

Self-measurement of blood pressure (BP) at home (HBP) has been recognized as a useful tool for accurate diagnosis and treatment of hypertension. Previous reports have indicated that HBP is correlated with target-organ damage, and predict the prognosis of hypertension better than casual-screening BP (CBP).[1,2]

The measurement of BP outside medical settings has identified a subgroup of individuals with white-coat hypertension (WCHT)[3] who have persistently elevated CBP but normal HBP or ambulatory BP (ABP) levels, and a subgroup of individuals with masked hypertension (MHT)[4] who have normal CBP but elevated HBP or ambulatory BP levels. The clinical significance of WCHT in relation to cardiovascular disease risk is controversial.[5,6] Similarly, there is little conclusive evidence about the association between WCHT and metabolic abnormalities.[7]

Oral glucose tolerance test (OGTT) is widely used for diagnosing diabetes mellitus (DM). Fasting glucose level is insufficient to diagnose DM; however, measuring glucose level 2-h after an oral glucose load has strong predictive power for cardiovascular disease.[8–10] Although several studies have shown the association between OGTT and CBP,[11,12] the association between OGTT and HBP remains unclear. Moreover, the relationship of WCHT and MHT with glucose metabolism is undetermined. Therefore, the aim of this study was to determine the relationship between glucose metabolism and WCHT, as well as MHT on the basis of HBP in the general population.

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METHODS

Study population

This investigation is a part of a longitudinal observational study of HBP measurements among Ohasama residents that started in 1987. The socio-economic and demographic characteristics of this region and full details of the project have been described elsewhere.[13] Between 2000 and 2008, we contacted all 4809 individuals aged ⩾35 years in four districts of Ohasama town. Those who were not at home during the normal working hours of the study nurses (n=1298) and those hospitalized (n=192) or incapacitated (n=120) were not eligible. Of the remaining 3199 residents, 2181 (68%) gave written, informed consent to participate in the HBP measurement program. Of those, 700 individuals (19%) voluntarily participated in the OGTT. We excluded those treated with antidiabetic (n=11) and antihypertensive agents (n=223) from this analysis. The total number of participants statistically analyzed was thus 466. The study protocol was approved by the Institutional Review Board of Tohoku University School of Medicine, Sendai, Japan, and by the Department of Health of the Ohasama Town Government.

BP measurement

HBP was measured using the semi-automatic HEM-747IC-N or HEM701C (Omron Healthcare, Kyoto, Japan), a device based on the cuff-oscillometric method that generates a digital display of both systolic and diastolic BP values.[14] Physicians and public health nurses instructed the participants on how to use the device and record HBP results. The participants then measured their own BP once in the morning, in the sitting position within 1 h after awaking and after 2 min of rest and recorded such measurements for 4 weeks. Although many participants measured their HBP values twice or more per occasion, we used the first value from each measurement in our analysis to exclude individual selection bias.[15] HBP was defined as the mean of all measurements. The mean number of total HBP measurements was 24. CBP measurements were taken after at least 2 min of rest, twice consecutively, using an automatic device (HEM-907, Omron Healthcare) before OGTT. The average of two consecutive readings from each individual was used as CBP. The HBP and CBP measuring devices used in this study have been validated[14,16,17] and meet the criteria established by the Association for the Advancement of Medical Instrumentation.[18]

OGTT and other information

OGTT was carried out using a 75-g glucose-equivalent carbohydrate load (Trelan G; Ajinomoto Pharma, Tokyo, Japan) after the fasting blood samples were collected. Blood samples were drawn at 60 min (1 h) and 120 min (2 h), and glucose levels and insulin were measured. Information on the use of antihypertensive, hyperlipidemic and diabetic medications at baseline was obtained from interviews conducted at the time of OGTT, from records of annual health checkups and from records of Ohasama Hospital. Serum adiponectin was measured using a latex particle-enhanced turbidimetric immunoassay (SRL, Tokyo, Japan).

Classification of groups

Participants were classified into four groups (normotension (NT), WCHT, MHT and sustained hypertension (SHT)) on the basis of their HBP and CBP levels: NT, with systolic CBP < 140 mm Hg and diastolic CBP < 90 mm Hg, and systolic HBP < 135 mm Hg and diastolic HBP < 85 mm Hg; WCHT, with systolic CBP ⩾ 140 mm Hg or diastolic CBP ⩾ 90 mm Hg or both, and systolic HBP < 135 mm Hg and diastolic HBP < 85 mm Hg; MHT, with systolic CBP < 140 mm Hg and diastolic CBP < 90 mm Hg, and systolic HBP ⩾ 135 mm Hg or diastolic HBP ⩾ 85 mm Hg or both; and SHT, with systolic CBP ⩾ 140 mm Hg or diastolic CBP ⩾ 90 mm Hg or both, and systolic HBP ⩾ 135 mm Hg or diastolic HBP ⩾ 85 mm Hg or both (Figure 1). Cutoff values were derived from several guidelines.[19–21]

On the basis of OGTT, subjects were classified as having DM, impaired glucose intolerance, impaired fasting glucose or normal glucose tolerance according to the World Health Organization classification[22] (Figure 2).

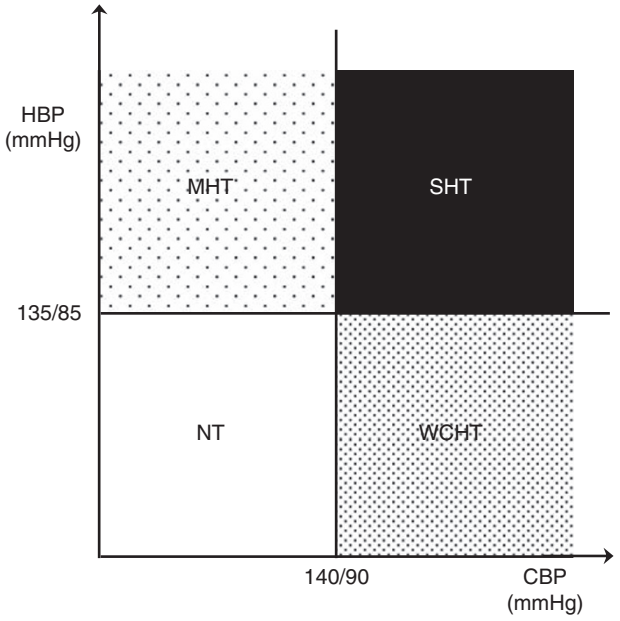

Figure 1 Distribution of subjects classified into four groups on the basis of HBP and CBP levels. CBP, casual-screening blood pressure; HBP, home blood pressure; MHT, masked hypertension; NT, normotension; SHT, sustained hypertension; WCHT, white-coat hypertension.

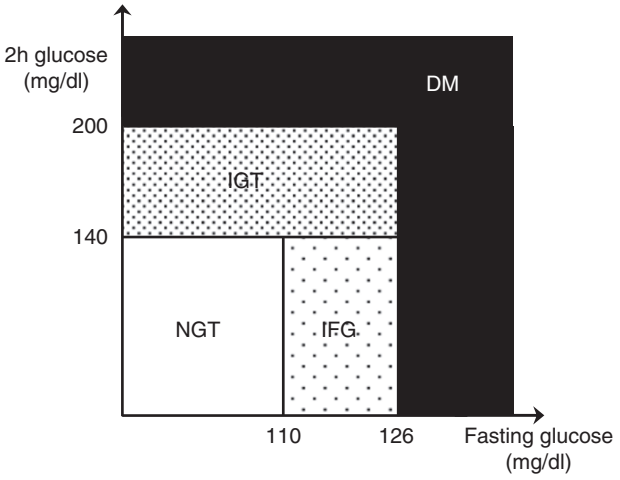

Figure 2 Distribution of subjects classified into four groups on the basis of fasting glucose and 2-h glucose level, which were determined by OGTT. DM, diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

Data analysis

Dyslipidemia was defined in accordance with criteria of the Japanese metabolic syndrome[23] as low high-density lipoprotein-cholesterol (<40 mg per 100 ml (1.03 mmol l^{-1})), high triglyceride (⩾150 mg per 100 ml (1.68 mmol l^{-1})) and/or the use of antilipidemic treatment. Area under the blood concentration time curve was calculated using fasting plasma glucose, 1-h glucose and 2-h glucose by quadrature by parts (area under the blood concentration time curve=(fasting plasma glucose+1-h glucose)×0.5+(1-h glucose+2-h glucose)×0.5). The homeostasis model assessment-insulin resistance index (HOMA-IR) was calculated using the following formula: HOMA-IR=fasting glucose (mg per 100 ml)×fasting insulin (μUnits per ml)/405. Insulin sensitivity was determined by the Matsuda DeFronzo index based on the following formula: 10 000/sqrt (fasting glucose (mg per 100 ml)×fasting insulin (μUnits per ml)) (mean glucose (mg per 100 ml)×mean insulin (μUnits per ml)).[24]

All data are expressed as means ± s.d. Variables were compared using Fisher's exact test, ANOVA (analysis of variance) or ANCOVA (analysis of covariance), followed by Tukey's multiple comparison test. Associations between indices for glucose metabolism and BPs as continuous variables were examined with multiple regression analysis adjusted by age, body mass index, dyslipidemia, history of cardiovascular disease, drinking habit and smoking habit. Statistical significance was established at $P<0.05$. All statistical calculations were carried out using the SAS system (version 9.1, SAS Institute, Cary, NC, USA).

RESULTS

The characteristics of the study participants are given in Table 1. The mean age was 61.0 ± 9.6 years and the proportion of men and women was 29:71. Mean systolic/diastolic CBP and HBP values were 131.3 ± 18.3/76.1 ± 11.2 mm Hg and 122.3 ± 15.0/74.5 ± 9.0 mm Hg, respectively. Of the 466 subjects, 268 were classified as having NT, 49 were classified as having MHT, 90 were classified as having WCHT and the remaining 59 were classified as having SHT. Both CBP and HBP values in the NT group were significantly lower those in than the other groups. Subjects in the NT group tended to be younger than those in the other categories of BP classification.

The relationships between glucose metabolism and each BP group were analyzed using ANCOVA (Table 2). Among subjects with WCHT and SHT, significantly higher glucose levels and HOMA-IR values and significantly lower Matsuda DeFronzo index values were observed when compared with NT (all $P<0.03$). Among those with MHT, there were no indices for glucose metabolism, which showed significant

Table 1 Characteristics of study participants

	All subjects	*Subjects with NT*	*Subjects with MHT*	*Subjects with WCHT*	*Subjects with SHT*	*ANOVA* P-*value*
Number of subjects (*n*)	466	268	49	90	59	—
Gender (women, %)	71.0	77.2	49.0	76.7	52.5	<0.0001
Age (years)	61.0 ± 9.6	59.8 ± 9.7	63.4 ± 9.7	62.4 ± 8.7	62.4 ± 10.0	0.02
Body mass index (kg m^{-2})	23.3 ± 3.2	22.7 ± 3.0	24.0 ± 3.6*	23.5 ± 2.8	24.9 ± 3.6*,‡	<0.0001
Height (cm)	55.6 ± 10.3	54.1 ± 9.2	59.6 ± 13.9	54.6 ± 8.7†	60.2 ± 11.6	0.02
Weight (kg)	154.2 ± 8.5	154.1 ± 8.1	156.8 ± 10.4*	152.3 ± 7.9†	155.2 ± 8.8*,‡	<0.0001
Systolic HBP (mm Hg)	122.3 ± 15.0	114.4 ± 10.7	139.5 ± 8.9*	122.5 ± 8.5*,†	143.4 ± 10.3*,‡	<0.0001
Diastolic HBP (mm Hg)	74.5 ± 9.0	70.3 ± 6.9	84.6 ± 6.8*	74.3 ± 5.7*,†	85.4 ± 7.1*,‡	<0.0001
Home heart rate (b.p.m.)	65.2 ± 7.7	64.6 ± 7.1	66.9 ± 8.1	66.1 ± 7.6	64.9 ± 9.5	0.2
Systolic CBP (mm Hg)	131.3 ± 18.3	120.8 ± 12.2	127.1 ± 9.2*	149.4 ± 9.1*,†	154.5 ± 14.4*,†,‡	<0.0001
Diastolic CBP (mm Hg)	76.1 ± 11.2	70.6 ± 8.5	75.5 ± 7.8*	85.2 ± 9.3*,†	87.7 ± 9.5*,†	<0.0001
HDL (mg per 100 ml)	62.3 ± 15.4	63.0 ± 16.0	59.2 ± 14.8	62.5 ± 14.2	61.6 ± 14.8	0.4
Triglyceride (mg per 100 ml)	100.3 ± 62.5	89.8 ± 52.7	115.6 ± 63.5*	109.1 ± 74.4	122.1 ± 73.5*	0.0002
Drinking habit (%)	41.9	40.7	59.2	26.7	55.9	0.0002
Smoking habit (%)	13.7	12.3	30.6	7.8	15.3	0.004
Dyslipidemia (%)	19.1	15.3	28.6	18.9	28.8	0.03
[a]IFG(%)	5.4	2.2	6.1	11.1	10.2	0.002
[a]IGT(%)	20.0	17.2	18.4	24.4	27.1	0.2
[a]Diabetes mellitus (%)	6.9	3.7	6.1	8.9	18.6	0.001
Past history of CVD (%)	2.8	1.9	8.2	1.1	5.1	0.04

Abbreviations: ANOVA, analysis of variance; CBP, casual-screening blood pressure; CVD, cardiovascular disease; HBP, home blood pressure; HDL, high-density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose intolerance; MHT, masked hypertension; NT, normotension; SHT, sustained hypertension; WCHT, white-coat hypertension.
*$P<0.05$ compared with NT.
†$P<0.05$ compared with MHT.
‡$P<0.05$ compared with WCHT.
[a]IFG, IGT and diabetes mellitus were defined by the oral glucose tolerance test.

Table 2 Variables in relation to glucose metabolism

	All subjects	*Subjects with NT*	*Subjects with MHT*	*Subjects with WCHT*	*Subjects with SHT*	*ANCOVA* P-*value*
Number of subjects (*n*)	466	268	49	90	59	—
Fasting plasma glucose (mg per 100 ml)	95.1 ± 10.9	93.0 ± 9.7	95.1 ± 10.3	98.7 ± 12.3*	99.1 ± 11.9*	0.0003
One-hour glucose (mg per 100 ml)	157.1 ± 52.6	148.0 ± 51.0	156.2 ± 44.1	171.4 ± 49.1*	177.7 ± 61.4*	0.001
Two-hour glucose (mg per 100 ml)	126.7 ± 43.1	119.7 ± 37.6	121.6 ± 39.3	136.8 ± 50.1*	146.9 ± 49.4*,†	0.0007
Glucose AUC_{0-120} (mg per 100 ml h)	268.0 ± 71.5	254.3 ± 67.1	264.6 ± 60.3	289.2 ± 71.0*	300.7 ± 82.6*,†	0.0002
Δ60 glucose (mg per 100 ml h)	62.0 ± 48.0	55.0 ± 47.2	61.0 ± 39.3	72.7 ± 44.6*	78.6 ± 56.6*	0.01
Δ120 glucose (mg per 100 ml h)	31.6 ± 39.3	26.7 ± 34.5	26.5 ± 36.8	38.1 ± 45.1	47.9 ± 46.7*,†	0.008
HOMA	1.32 ± 0.86	1.20 ± 0.71	1.33 ± 1.09	1.47 ± 0.81*	1.66 ± 1.15*	0.03
MDI	8.89 ± 4.54	9.68 ± 4.87	9.53 ± 4.78	7.25 ± 3.13*,†	7.26 ± 3.54*,†	0.0009

Abbreviations: ANCOVA, analysis of covariance; AUC_{0-120}, area under the blood concentration time curve; HOMA, homeostasis model assessment; MDI, Matsuda DeFronzo index; MHT, masked hypertension; NT, normotension; SHT, sustained hypertension; WCHT, white-coat hypertension.
Adjusted for sex, age, body mass index, dyslipidemia, history of cardiovascular disease, drinking habit and smoking habit.
Δ60 glucose=1-h glucose—fasting plasma glucose; Δ120 glucose=2-h glucose—fasting plasma glucose.
*$P<0.05$ compared with NT.
†$P<0.05$ compared with MHT.

Table 3 Variables in relation to glucose metabolism according to sex

	All subjects	*Subjects with NT*	*Subjects with MHT*	*Subjects with WCHT*	*Subjects with SHT*	*ANCOVA* P-*value*
Men						
Number of subjects (*n*)	135	61	25	21	28	
Age (years)	61.2 ± 9.1	61.0 ± 9.4	59.2 ± 8.7	63.8 ± 6.2	61.5 ± 10.6	0.4
Fasting plasma glucose (mg per 100 ml)	97.4 ± 10.9	96.1 ± 10.4	96.2 ± 12.4	98.5 ± 8.4	100.5 ± 11.9	0.6
One-hour glucose (mg per 100 ml)	168.5 ± 58.5	164.7 ± 61.5	164.5 ± 48.5	165.2 ± 52.3	182.6 ± 64.9	0.7
Two-hour glucose (mg per 100 ml)	129.0 ± 47.4	124.9 ± 46.8	130.2 ± 44.4	124.6 ± 39.4	140.1 ± 56.4	0.7
Glucose AUC_{0-120} (mg per 100 ml h)	281.7 ± 78.2	275.2 ± 80.8	277.7 ± 70.0	276.8 ± 65.1	302.9 ± 88.0	0.7
Δ60 glucose (mg per 100 ml h)	71.1 ± 54.2	68.7 ± 57.9	68.2 ± 42.3	66.7 ± 49.2	82.0 ± 59.9	0.8
Δ120 glucose (mg per 100 ml h)	31.6 ± 43.6	28.9 ± 42.2	34.0 ± 40.8	26.1 ± 39.4	39.6 ± 52.1	0.8
HOMA	1.31 ± 0.96	1.15 ± 0.62	1.33 ± 1.15	1.29 ± 0.81	1.64 ± 1.37	0.3
MDI	9.76 ± 5.29	11.0 ± 6.11	10.1 ± 5.05	8.51 ± 3.83	7.75 ± 3.62*	0.03
Women						
Number of subjects (*n*)	331	207	24	69	31	
Age (years)	61.0 ± 9.8	59.5 ± 9.8	67.7 ± 8.8*	62.0 ± 9.3	63.3 ± 9.5	0.0003
Fasting plasma glucose (mg per 100 ml)	94.2 ± 10.7	92.1 ± 9.3	94.0 ± 7.6	98.7 ± 13.3*	97.7 ± 12.0*	0.0005
One-hour glucose (mg per 100 ml)	152.5 ± 49.3	143.0 ± 46.5	147.5 ± 38.1	173.3 ± 48.3*	173.2 ± 58.7*	0.0006
Two-hour glucose (mg per 100 ml)	125.7 ± 41.3	118.2 ± 34.4	112.7 ± 31.6	140.5 ± 52.6*,†	153.1 ± 42.1*,†	<0.0001
Glucose AUC_{0-120} (mg per 100 ml h)	262.4 ± 67.9	248.2 ± 61.4	250.8 ± 45.8	292.9 ± 72.7*	298.7 ± 78.8*	<0.0001
Δ60 glucose (mg per 100 ml h)	58.3 ± 44.8	50.9 ± 42.9	53.5 ± 35.2	74.6 ± 43.4*	75.5 ± 54.2*	0.005
Δ120 glucose (mg per 100 ml h)	31.5 ± 37.5	26.1 ± 32.0	18.7 ± 30.9	41.8 ± 46.3*,†	55.4 ± 40.6*,†	0.0002
HOMA	1.33 ± 0.81	1.21 ± 0.74	1.33 ± 1.04	1.52 ± 0.82*	1.67 ± 0.92*	0.2
MDI	8.53 ± 4.16	9.29 ± 4.38	8.98 ± 4.52	6.86 ± 2.80*	6.83 ± 3.46*	0.3

Abbreviations: ANCOVA, analysis of covariance; AUC_{0-120}, area under the blood concentration time curve; HOMA, homeostasis model assessment; MDI, Matsuda DeFronzo index; MHT, masked hypertension; NT, normotension; SHT, sustained hypertension; WCHT, white-coat hypertension.
Adjusted for age, body mass index, dyslipidemia, history of cardiovascular disease, drinking habit and smoking habit.
Δ60 glucose=1-h glucose—fasting plasma glucose; Δ120 glucose=2-h glucose—fasting plasma glucose.
* $P<0.05$ compared with NT.
† $P<0.05$ compared with MHT.

differences from those in subjects with NT. Similarly, no significant difference was observed between subjects with WCHT and those with SHT. Further analysis in subjects in which serum adiponectin levels were measured (n=167) showed that significantly lower adiponectin levels were observed in subjects with WCHT (10.5 ± 6.0) when compared with those with NT (14.7 ± 6.7) (P=0.044). Similar trends were observed only in women (data not shown).

The results in which men and women were analyzed separately are shown in Table 3. There were no significant differences in fasting glucose levels, 2-h glucose levels, HOMA-IR and the Matsuda DeFronzo index between MHT and NT regardless of sex. For women with WCHT and SHT, glucose levels were significantly higher than those with NT. Meanwhile, no significant differences of glucose levels among BP groups were observed in men. HOMA-IR in women was significantly higher in individuals with WCHT and SHT (1.5 ± 0.8 and 1.7 ± 0.9, respectively) than in those with NT (1.2 ± 0.7), whereas HOMA-IR in men did not differ among the four BP groups. Similar results were observed with regard to the Matsuda DeFronzo index, although the Matsuda DeFronzo index in men was significantly higher in individuals with SHT (7.7 ± 3.6) than in those with NT (11.0 ± 6.1). However, there was no significant interaction between BP groups and sex in relation to glucose levels, HOMA-IR and the Matsuda DeFronzo index (all $P>0.2$).

The results of multiple regression analysis indicated that CBP values were significantly associated with several indices for glucose metabolism even adjusted by confounding factors. When systolic HBP and systolic CBP values were simultaneously included in the model (Table 4), systolic CBP, but not systolic HBP, was significantly associated with indices for glucose metabolism, especially with fasting plasma glucose (P=0.14 for systolic HBP, $P<0.0001$ for systolic CBP).

DISCUSSION

In this study, glucose levels in subjects with WCHT and SHT were significantly higher than those with NT. In a previous study, young subjects with WCHT tended to have metabolism dysregulation.[25] In a population-based study, individuals with WCHT showed impaired insulin sensitivity compared with normotensive subjects in their late middle age.[26] Sympathetic nervous system activity has been associated with the development of WCHT and with insulin resistance.[27,28] Furthermore, CBP values were reported to be positively correlated with HOMA-IR.[29] Central sympathetic hyperactivity has also reported to exist in WCHT in the clinical setting.[27] Although we have not investigated sympathetic nerve activities in this study, the strong relationship between CBP and glucose metabolisms would support the existence of sympathetic nervous system hyperactivity in individuals with WCHT and SHT.

In this study, significant correlations between glucose dysregulation and WCHT were not observed in men. Sympathetic nerve activity would differ between men and women with WCHT. However, to our knowledge, there was no previous study about the sympathetic nerve system for difference between men and women with WCHT. Thus we cannot explain this difference between men and women from the viewpoint of the sympathetic nerve system. Other factors would contribute to hyperglycemia in individuals with WCHT, whereas the result might be just by chance because of a small number of participants. The difference between men and women should be investigated on the basis of a large population.

Table 4 Independent relations between indices for glucose metabolism and BP as determined by multiple regression analysis

	HBP		*CBP*		*Sex*		*Age*		*BMI*		*Dyslipidemia*		*Drinking habit*		*Smoking habit*		
	β	*s.e.*	*β*	*s.e.*	*β*	*s.e.*	*β*	*s.e.*	*β*	*s.e.*	*β*	*s.e.*	*β*	*s.e.*	*β*	*s.e.*	R^2
Fasting plasma glucose (mg per 100 ml)	−0.060	0.040	0.168	0.031‡	2.180	1.364	0.116	0.06*	0.385	0.164*	1.406	1.274	−1.150	1.157*	−0.170	1.651	0.1227
One-hour glucose (mg per 100 ml)	0.094	0.198	0.416	0.152*	12.630	6.696	0.830	0.27†	0.880	0.806	8.043	6.254	4.134	5.682	−6.550	8.105	0.0962
Two-hour glucose (mg per 100 ml)	0.191	0.163	0.346	0.125*	4.129	5.513	0.348	0.22	1.533	0.664*	6.960	5.149	4.184	4.678	5.757	6.673	0.0899
Glucose AUC $_{0-120}$ (mg per 100 ml h)	0.160	0.267	0.673	0.205†	15.790	9.029	1.062	0.37†	1.839	1.087	12.230	8.432	5.650	7.661	−3.760	10.930	0.1112
Δ60 glucose (mg per 100 ml h)	0.153	0.183	0.248	0.140	10.460	6.187	0.714	0.25†	0.495	0.745	6.637	5.779	5.286	5.250	−6.380	7.489	0.0749
Δ120 glucose (mg per 100 ml h)	0.251	0.150	0.178	0.116	1.949	5.093	0.232	0.21	1.149	0.613	5.554	4.756	5.336	4.321	5.929	6.164	0.0640
HOMA	0.002	0.003	0.004	0.002	−0.030	0.103	−0.010	0†	0.090	0.012‡	0.226	0.096*	0.146	0.087	−0.050	0.125	0.1949
MDI	−0.010	0.016	−0.040	0.012†	0.332	0.529	0.019	0.02	−0.470	0.064‡	−1.440	0.494†	−1.570	0.449†	−1.330	0.640*	0.2459
[a]Adiponectin (μg ml^{-1})	−0.030	0.040	0.026	0.028	−4.730	1.239†	0.221	0.05‡	−0.740	0.146‡	−1.000	1.151	−1.030	1.025	−0.300	1.528	0.3758

Abbreviations: AUC_{0-120}, area under the blood concentration time curve; BMI, body mass index; BP, blood pressure; CBP, casual-screening blood pressure; HBP, home blood pressure; HOMA, homeostasis model assessment; MDI, Matsuda DeFronzo index.
*$P<0.05$, †$P<0.005$, ‡$P<0.0001$.
Δ60 glucose=1-h glucose—fasting plasma glucose; Δ120 glucose=2-h glucose—fasting plasma glucose.
[a]The number of subjects who have the data of adiponectin is 167.

The association between WCHT and the risk of cardiovascular disease is inconsistent. Although many reports have shown that the risk of cardiovascular disease in subjects with WCHT was comparable with NT,[6,30] our previous report indicated that WCHT is correlated with high risk for development of SHT and suggested that WCHT would carry a poor cardiovascular prognosis on a long-term basis.[31] The cumulative hazard for stroke in the WCHT group was equal to that of the ambulatory hypertensive group according to the results of a meta-analysis of prospective studies, including the Ohasama study.[32] Thus, dysregulation of glucose metabolism might be associated with WCHT, which is a risk factor for cardiovascular disease in the long term. Diabetic nephropathy and diabetic retinopathy were more progressive in diabetic individuals with WCHT than in those with NT.[33] It would be useful for individuals with WCHT to undergo an OGTT to detect dysregulation of glucose metabolism in the early stages. Furthermore, early detection and prevention for progression from WCHT to SHT should be monitored by consecutive measurements of HBP.

Significantly low adiponectin levels were observed in subjects with WCHT compared with those with NT. The observations also support the involvement of insulin resistance in glucose dysmetabolism. The role of adipocytokine might explain sex differences for glucose metabolism as this tendency was observed especially in women; however, the number of subjects was very small especially when men and women were analyzed separately. The association between adipocytokine or sex difference and glucose metabolism should be investigated with a large number of participants.

No significant difference in indices for glucose metabolism was observed between subjects with WCHT and those with SHT. However, the tendency of low adiponectin levels was observed in subjects with WCHT compared with those with SHT. Although there were small (although not statistically significant) differences in indices for glucose metabolism between WCHT and SHT, significantly low weight and body mass index were observed in subjects with WCHT when compared with those with SHT. Despite this, the level of adiponectin in subjects with WCHT was lower and the level of glucose metabolism dysregulation was comparable when compared with those with SHT. Thus, we believe that WCHT is not comparable with SHT and might not be a safe condition.

There was no specific tendency for glucose metabolism in MHT in this study. In previous studies, fasting glucose levels were reported to be significantly higher in the MHT group than in the NT group, and those in the MHT group were similar to the SHT group.[7,34] These results were inconsistent with our findings that glucose metabolism of subjects with MHT was comparable with those with NT. The most likely explanation is that individuals treated with antihypertensive medication were excluded from this study. Several previous studies in relation to the prognosis of MHT consisted of subjects treated with antihypertensive medication[7,35] or included subjects both with and without antihypertensive medication.[36] Although the high risk of cerebrovascular and cardiovascular disease in subjects with MHT has been established by these previous studies, the risk for individuals with MHT without antihypertensive medication would be a separate concern. Exclusion of subjects taking antihypertensive medication in the current study resulted in an insufficient number of subjects in each BP category and might lead to insufficient statistical power to draw a conclusion. Thus, further research including individuals who use antihypertensive medication would be necessary to clarify the association between MHT and dysregulation of glucose metabolism.

It should also be noted that subjects who were previously diagnosed with DM and those treated with antidiabetic agents did not participate

in this study. Several studies including our previous study have shown that many subjects with MHT had a history of DM[37] or were prescribed antidiabetic treatment.[38,39] In this study, subjects with MHT might have been excessively excluded, and thus glucose levels of the MHT group might be underestimated and create a weak association between MHT and glucose levels. The possibility of selection bias should be considered when generalizing the report findings. Furthermore, the number of subjects with MHT (n=49) in this study was relatively small, which resulted in an insufficient statistical power; the association between MHT and the dysregulation of glucose metabolism remain a matter for debate. It is also well known that patients with MHT have a greater frequency of target-organ damage[34,37] and have a greater risk of cardiovascular disease.[36] Thus, it is important to promote further research with a large number of subjects, including those with DM to confirm the association between dysregulation of glucose metabolism and MHT.

According to the multiple regression model, CBP would be more useful for predicting dysregulation of glucose metabolism or insulin resistance than HBP. In the previous study, it was established that HBP value has a stronger predictive power for target-organ damage, morbidity and mortality than has the CBP value.[1,2] Glucose metabolism is also treated as a risk factor for cardiovascular diseases.[9,10] It seems reasonable to suppose that HBP and glucose metabolism would affect to cardiovascular diseases independently. Further follow-up studies are required to investigate long-term prognosis in terms of comparing BP information and glucose metabolism.

There were several limitations in this study. OGTT data were obtained at only one measurement in one occasion. If we carry out OGTT twice or more, the classification based on OGTT might be changed. We excluded patients with DM or with a history of DM. The study participants might not be the same as the entire population of Ohasama, and study participants' potential awareness of health concerns would be higher than the other residents in the general population. Thus, the possibility of selection bias needs to be considered when generalizing the present findings. Furthermore, this study included a comparably small number of men without data of participants' detailed lifestyle, although sex-specific associations were observed. Women have reported to have a greater tendency to be influenced by the white-coat effect than men,[40,41] and decreased glucose tolerance related to poor lifestyle choices was more common in women than in men.[42] Therefore, further prospective studies based on a sufficient number of subjects with detailed information are required to overcome these limitations.

In conclusion, strong associations between dysregulation of glucose metabolism and WCHT were observed in this study. Our findings suggest that dysregulation of glucose metabolism might contribute to the increase in the long-term risk of poor prognosis for subjects with WCHT. It is useful for individuals with WCHT to undergo OGTT to detect early stages of dysregulation of glucose metabolism. Consecutive measurements of HBP would also be important to detect and to prevent progression from WCHT to SHT.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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