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Usefulness of Morning Home Blood Pressure Measurements in Non-Obese and Obese Japanese Patients with Type 2 Diabetes Mellitus: Results of a 10-Years, Prospective and Longitudinal Study

Kyuzi Kamoi*

Department of Medicine, Ojiya General Hospital, Ojiya, Niigata 947-8601, Japan

***Corresponding author:** *Dr. Kyuzi Kamoi, Department of Medicine, Ojiya General Hospital 3-4-36 Hanazono Nagaoka, Niigata 940-0845, Japan, Tel: +81-0258-36-3986; Fax: +81-0258-36-3986; E-mail: kkam-int@echigo.ne.jp*

Abstract

Aim: It was demonstrated that home blood pressure (HBP) has a stronger predictive power for death, micro- and macrovascular complications than clinic blood pressure (CBP) in patients with type 2 diabetes mellitus (T2DM). This study investigated which of these measurements offers predicatively stronger power for outcomes over 10 years in non-obese and obese patients with T2DM.

Methods: At baseline and end-point, 400 Japanese patients with T2DM were classified as having non-obesity or obesity with hypertension or normotension. Body mass index with < 25.0 kg/m^2 and ≧25.0 kg/m^2, and same thresholds of systolic blood pressure with ≥ 130 mmHg and < 130 mmHg are defined as non-obesity and obesity, and hypertensions and normotensions, respectively. Mean survey duration was 95 months. Primary and secondary outcomes were death, and new or worsened micro- and macrovascular events, respectively. Differences in outcomes for end-point were analyzed using Kaplan-Meier survival curves and log-rank testing. Associated risk factors were assessed using Cox proportional hazards analysis.

Results: Based on HBP, incidences in death, and micro-and macrovascular events were significantly higher in obesity than in non-obesity. However, based on CBP, there were no significant differences of incidences in their vascular events between obesity and non-obesity. One risk-factor associated with obese patients with elevated HBP was therapy for hypertension.

Conclusion: this 10-yearsstudy of patients with T2DM demonstrated that elevated HBP is more predictive death and micro- and macrovascular complications in obesity than in non-obesity.

Abbreviations: BP: Blood pressure, BMI: Body mass index, CBP: Clinic blood pressure, CI: Confidence intervals, CHD: Coronary heart diseases, CVD: Cerebrovascular diseases, DBP: Diastolic blood pressure, HbA1c: Glycated hemoglobin A1c, HBP: Home blood pressure, HDL: High density lipoprotein, HT: Hypertension, LDL: Low density lipoprotein, NGSP: National gycohemoglobin standardization program, NT: Normotension, PAO: Peripheral artery obstruction, SBP: Systolic blood pressure, T2DM: Type 2 diabetes mellitus, TC: Total cholesterol, TG: Triglyceride, UAER: Urinary albumin excretion rate

Introduction

It was demonstrated that home blood pressure (HBP) measured in the morning at upon-awakening has better predictive power for death and micro- and macrovascular complications in patients with type 2 diabetes mellitus (T2DM) than casual/clinic blood pressure (CBP) measured [1-3].

Since early time, it is known that obesity in patients with T2DM has a risk-factor for hypertension (HT) measured on CBP [4-6], which influences vascular complications. The study examined whether CBP or HBP measurements provided stronger predictive power for outcomes by comparing cumulative events between non-obese and obese patients with T2DM with either HT or normotension (NT) over 10 years.

Materials and Methods

Subjects

Subjects comprised 400 Japanese patients with T2DM enrolled between 1999 and 2005 [3], who were divided into two groups with non-obesity and obesity [7].

Subjects were followed up for all-cause morbidity and mortality. All participants visited our clinic regularly and were followed until March 31, 2013. T2DM was diagnosed according to World Health Organization criteria [8], which is required that glycated hemoglobin (HbA1c) level is greater than 6.5% as national glycohemoglobin standardization program (NGSP). All HbA1c values were converted to NGSP values according to the Japan Diabetes Society [9].

Baseline characteristics of participants have been described as table 1. At the beginning of study, 329 patients (82%) were receiving treatment with oral hypoglycemic drugs and/or insulin regimens for T2DM and 196 patients (49%) were receiving treatment with various anti-hypertensive drugs for HT [3]. All patients were fully informed on purposes and procedures for the study and provided oral consent at enrolment and the approval of local ethical committee. This study was a registered clinical trial (Clinical Trial reg. no. NCT00760110)

Methods

Chemical laboratory data: All chemical laboratory data were obtained at each clinic visit in a non-fasting state for each 3-month. A single specimen was used to assess levels of blood HbA1c, serum creatinine, serum lipid and urinary albumin excretion rate (UAER) based on 2009 guidelines of the American Diabetes Association [10]. Briefly, HbA1c was measured by high-performance liquid

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Table 1: Clinical characteristics of non-obese and obese patients with type 2 diabetes mellitus on blood pressure measured at basal and end-point, respectively.

Variable	Obese patients		Non-Obese patients		P value	
	Basal	End-point	Basal	End-point	Basal	End-point
	(n = 153)	(n = 116)	(n = 247)	(n = 284)		
Age (years)	64 ± 10	71 ± 10**	65 ± 9	73 ± 10**	0.306	0.07
Gender (Male/Female)	78/75	63/53	135/112	150/134	1.000	1.000
	(51)/(49)	(54)/(46)	(55)/(45)	(53)/(47)	1.000	1.000
Diabetes duration (years)	14 ± 11	22 ± 8**	15 ± 11	23 ± 12**	0.377	0.41
BMI (kg/m^2)	27 ± 3	28 ± 3	22 ± 3	22 ± 2	< 0.001	< 0.001
	25 - 39	25.-39	15 - 24	15 - 24.9		
Blood pressure (mmHg)						
Clinic systolic pressure	147 ± 27	134 ± 19**	142 ± 24	129 ± 14**	0.054	0.001
Clinic diastolic pressure	86 ± 16	75 ± 15**	84 ± 15	73 ±18**	0.208	0.200
Morning systolic pressure	146 ± 22	131 ± 18**	139 ± 23	125 ± 84**	0.002	0.254
Morning diastolic pressure	83 ± 12	73 ± 13**	79 ± 12	70 ± 13**	0.001	0.037
Laboratory variables						
HbA1c(NGSP) (%)	7.2 ± 1.1	7.3 ± 1.1	7.0 ± 1.0	7.0 ± 1.1	0.062	0.014
Triglyceride (mg/dl)	168 ± 143	148 ± 11	139 ± 87	116 ± 79**	0.025	0.001
Total cholesterol (mg/dl)	200± 29	189 ± 34	197± 34	185 ± 34**	0.348	0.289
LDL-cholesterol (mg/dl)	112 ± 27	108 ± 25	109 ± 31	102 ± 25**	0.324	0.03
HDL-cholesterol (mg/dl)	58 ± 20	53 ± 13	61 ± 18	59 ± 13	0.922	0.001
Serum creatinine (mg/dl)	0.8 ± 0.3	0.9 ± 0.5	0.8 ± 0.3	0.9 ± 0.5	1.000	1.000
UAER (mg/g creatinine)	243 ± 808	270 ± 795	100 ± 299	135 ± 795	0.037	0.124
Medical events						
Microvascular complications	105 (67)	105 (91)*	137 (55)	137 (48)*	1.000	1.000
Retinopathy	66 (43)	47 (41)	82 (29)	92 (32)	1.000	1.000
Nor/simp/pre/pro	87/39/7/20	69/23/4/20	177/42/7/21	192/51/8/33		
Nephropathy	70 (46)	46 (40)*	103 (42)	46 (16)**	1.000	1.000
Nor/simp/mac/dial	76/57/20/0	70/32/11/3	144/89/14/0	175/92/16/1		
Neuropathy	16 (10)	12 (10)	19 (8)	20 (7)	1.000	1.000
Macrovascular complications	39 (25)	19 (16)**	57 (23)	31 (11)**	1.000	1.000
Medical treatment						
Therapy for hypertension	87 (57)	76 (66)	107 (43)	175 (63)**	1.000	1.000
Therapy of medicines for diabetes mellitus	129 (84)	108 (91)*	203 (82)	262 (93)*	1.000	1.000
Non-insulin/insulin	101/65	90/69	147/96	220/134		
	(66)/(42)	(78)/(59)*	(60)/(39)	(77)/(47)*	1.000	1.000
Therapy for dyslipidemia	64 (42)	45 (39)	66 (27)	86 (30)	1.000	1.000
Therapy for hypercoagulation	41 (27)	29 (25)	48 (19)	57 (20)	1.000	1.000
Therapies for others	49 (32)	25 (22)	69 (28)	80 (28)	1.000	1.000

Clinical characteristics of non-obese and obese patients with type 2 diabetes mellitus on blood pressure measured at basal and end-points were shown, respectively. The non-obesity and obesity were defined by the criteria of Japan Society for the Study of Obesity. Body mass Index with < 25.0 kg/m^2 was defined as non-obesity, whereas BMI with ≧25.0 kg/m^2 was defined as obesity. Blood pressure using clinic method (CBP) and home method (HBP) measured once in each clinic visit and in the same morning at each clinic visit within 10 minutes after awakening in the sitting position were measured at basal and end-point, respectively, as shown as the same threshold of normotension with of less than 130 mmHg measurements in morning HBP and CBP. Number in parenthesis represents the percent ratio of each variable to patients participated in each group. Differences in the mean of each variable between non-obese and obese patients at basal and end-point were statistically evaluated by unpaired Student t test with or without Welch's correction.* and ** showed the values of P < 0.05 and P < 0.01 of each variable in groups of basal vs. end-point, respectively. P value (Basal and Endpoint) showed the statistical difference in each variable in patients with non-obesity and obesity at basal and end-point, respectively. Two tailed values of P < 0.05 were defined as statistically significant.

Abbreviation: BMI: Body mass index, HDL: High density lipoprotein, LDL: Low density lipoprotein, NGSP: National glycohemoglobin standardization program, UAER: Urinary albumin excretion rate, Nor-normal retinopathy or normal albuminuria, simp-simple retinopathy or simple albuminuria, pre-preproliferative retinopathy, pro-proliferative retinopathy, mac-macro albuminuria, dia-dialysis.

chromatography [1-3,11] and expressed as NGSP equivalent [9]. Serum levels of creatinine (mg/dl) and triglyceride (TG) (mg/dl) were measured by enzyme color methods [1-3,11]. Serum levels of total cholesterol (TC) (mg/dl), high density lipoprotein (HDL) (mg/dl) and low density lipoprotein (LDL)(mg/dl) were measured by direct methods [1-3,11]. Albumin concentration in random spot urine was measured by latex agglutination photometric immunoassay method [1-3,11]. Micro albuminuria and clinical albuminuria were defined as UAER ≥ 30 mg/g creatinine and ≥ 300 mg/g creatinine, respectively [10].

BMI: A definition of obesity on BMI is different between the Japan, and the U.S.A. and the Europe [7]. In the Japan, < 25.0 kg/m^2 and ≧25.0 kg/m^2 in BMI are defined as non-obesity and obesity, respectively, whereas in the USA and the Europe, from ≧25.0 kg/m^2 to < 30.0 kg/m^2 in BMI is defined as overweight [7].

Blood Pressure: CBP and HBP were assessed for the values measured once in each clinic visit and in the same morning at each clinic visit within 10 minutes after awakening in the sitting position, respectively [1,3]. Systolic blood pressure (systolic BP) with ≥ 130 mmHg was defined as HT of CBP or HBP, whereas systolic BP with < 130 mmHg was defined as NT of CBP or HBP [1]. The reason underlying that same threshold used for CBP and HBP was based on criteria of the 1999 World Health Organization-International Society of Hypertension guidelines [12], because of starting in 1999. HT of CBP and NT of HBP were defined as white coat HT [13-15], whereas NT of CBP and HT of HBP were defined as masked HT [13-15].

Based on CBP, subjects were divided into patients with HT and NT, and use of anti-hypertensive drug was determined in each group [3,13-15]. Sustained HT and sustained NT were defined from baseline to end-point, respectively [13-15]. In addition, based on HBP or CBP, subjects were divided into patients with HT and NT [3]. Recent guide-lines of HT indicated the different thresholds of NT, that is, systolic HBP is less than 125 mm and systolic CBP is less than 130 mmHg [1,13-15].

Microvascular complications: Microvascular complications included nephropathy, neuropathy and retinopathy. Severity of nephropathy was determined based on albuminuria using 4 categories: normal, 0 points; microalbuminuria, 1 point; clinical albuminuria, 2 points; and dialysis, 3 points [3]. Severity of neuropathy was categorized using 2 categories: normal, 0 point; sensorimotor distal symmetric polyneuropathy and/or cardiac autonomic neuropathy, 1 point. Severity of retinopathy was determined using 4 categories: normal, 0 point; simple, 1 point; pre-proliferative, 2 points; and proliferative, 3 points. Development of new, worsened, or improved micro angiopathy was defined according to a change of at least one step from baseline [1,16,17]

Macrovascular complications: Macrovascular complications included cerebrovascular disease (CVD), coronary heart disease (CHD) and peripheral artery obstruction (PAO). Severity of macrovascular events was categorized using 2 categories: normal, 0 point; and CVD, CHD or OAO, 1 point [3]. New, worsened (recurrent) or improved events were defined based on clinical manifestations and treatment with the study [1,16,17].

Study outcome at end-points: Outcome results considered only the first event in each subject [3]. Primary end-point was death from any cause [3]. Secondary end-points were improved or new and worsened micro- and macrovascular events [1,16,17]. The 6-month interval minimizes bias due to the fall or rise in BP [18].

Risk factors at end-point: Risk-factors at end-point in obese participants related to each outcome were determined, and therapy which was added to baseline therapy used for HT of HBP was recorded at end-point. For ethical reasons, patients were treated with various antihypertensive, anti-diabetic, anti-dyslipidemic, anti-hypercoagulation and anemic agents during course of the study by their own doctors [3].

Statistical analysis

Base-line and end-point of clinical characteristics: All results are presented as means ± SD. Mean values were compared by paired or unpaired student *t* test. Prevalence of micro- and macrovascular complications or medical treatments in non-obese and obese patients with or without HT at base- and end-points using CBP or HBP were compared [3,13-16]. Fisher's exact test was used, and then hazard ratios and 95% confidence intervals (CI) were calculated [3]. Further, in the obese patients, HT and NT at base-point for various vascular complications were calculated odds ratio and receiving operating characteristics (ROC) curve [1].

Relationship between morning home blood pressure at base- and end-point and body mass index: The relationships between morning HBP (mmHg) at base- and end-point and BMI (kg/m^2) were calculated by Pearson methods.

End-points and outcome measures: Differences in primary and secondary outcomes between non-obese and obese patients with HT and NT on CBP or HBP using the same threshold of NT were assessed by Kaplan-Meier survival curves and then compared by hazard rate using log-rank test [3,16], respectively. In addition, events in primary and secondary outcomes between HT and NT using the different thresholds of NT were assessed by the same methods mentioned above. The difference in overweight patients was examined by the same methods

Risk factor assessment for outcomes: Risk-factors determined to be statistically related to outcomes in the obese patients were assessed by Cox proportional hazard analysis [3].

All analysis was performed using the Prism version 6.03 software (GraphPad Software, CA, USA) and the Statistical Package for the Bioscience version 6.67 (ComWorks Co, Tokyo, Japan). Two-tailed values of $P < 0.05$ were considered statistically significant.

Results

Clinical characteristics of non-obese and obese patients with type 2 diabetes mellitus on blood pressure measured at base-and end-points

Body weight: On base- and end-points, 247 and 284 patients were fulfilled the criteria as non-obesity, respectively (Table 1), whereas 153 and 116 patients were fulfilled the criteria as obesity, respectively (Table 1), whose characteristics showed in table 1. At basal point, 205 (83%) of the 247 non-obese patients were continued and 42 (17%) of them changed into obesity, whereas 74 (48%) of the 153 obese patients were continued and 79 (52%) of them changed into non-obesity.

Blood pressure: Based on CBP, at base-point, 121 (49%) of the non-obese patients had HT and 126 (51%) of them had NT, whereas at end-point, 147 (51%) of the non-obese patients had HT and 137 (49%) of them had NT. On the hand, at base-point, 120 (78%) of the obese patients had HT and 33 (22%) of them had NT, whereas at end-point, 54 of the obese patients had HT and 62 of them had NT. In them of the non-obese patients, 89 (36%) with HT were continued until end-point and 63 (26%) with NT were sustained until end-point, whereas in them of the obese patients, 69 (45%) with HT were sustained and 25 (16%) with NT were continued. No significant differences in systolic or diastolic CBP at base- and end-points were shown between the non-obesity and the obesity (Table 1 and Table 2). Therapies for HT were insignificantly between the non-obesity and the obesity (Table 1 and Table 3).

Based on HBP, at base-point, 161 (65%) of the non-obese patients had HT and 86 (35%) of them had NT, whereas at end-point, 64 (23%) of the non-obese patients had HT and 220 (77%) of them had NT. On the hand, at base-point, 61 (40%) of the obese patients had HT and 92 (60%) of them had NT, whereas at end-point, 39 (34%) of the obese patients had HT and 77 (66%) of them had NT. Fifty one (21%) with HT in the non-obese patients at base-point were sustained and 70 (21%) with NT in them were continued. Whereas 55 (36%) with HT in the obese patients were sustained and 24 (16%) with NT in them were continued. Systolic or diastolic HBP level at base-point was significantly higher in the obesity than in the non-obesity (Table 1). Incidence of patients with masked HT at end-point were significantly ($P < 0.001$) greater in the obese patients than in the non-obese patients.

Relationships between HBP at basal and end-point and BMI: The

Table 2: Primary and secondary outcomes based on HBP* and CBP** measured at end-point in 116 obese patients with type 2 diabetes mellitus.

Outcome	Patient status: HBP* at end-point in 116 obese patients				Patient status: CBP** at end-point in 116 obese patients			
	Hypertension	Normotension	Hazard ratio	P	Hypertension	Normotension	Hazard ratio	P
	(n = 40)	(n = 76)	(95%CI)		(n = 54)	(n = 62)	(95%CI)	
Primary outcome								
Death	15	10	3.4 (1.8-9.9)	0.001	13	11	1.3 (0.6-3.0)	0.4904
Secondary outcome								
Microvascular complications	31	40	2.0 (1.7-4.9)	0.001	34	37	0.9 (0.5-1.7)	0.7110
Macrovascular complications	16	9	3.3 (1.6-8.2)	0.0024	13	12	1.2 (0.6-2.7)	0.5810

The obesity was defined by as the definition of the criteria of Japan Society for the Study of Obesity. Body mass Index (BMI) with ≧25.0 kg/m^2 was defined as obesity. The 400 patients in each group were classified as having obesity and hypertension or normotension according to values of blood pressure as same threshold of normotension with less than 130 mmHg of systolic blood pressure measured in the home (HBP*) and in the clinic (CBP**) at end-point, respectively. Differences in primary and secondary outcomes for events between obese patients with hypertension and normotension measured at end-point in each group were assessed using survival curves from the Kaplan-Meier method, and comparisons were analyzed using hazard ratio by the log-rank test. CI, confidence interval. Two-tailed values of $P < 0.05$ were defined as statistically significant.

Table 3: Risk factors for each outcome of events using morning hypertension at end-point in 116 obese patients with type 2 diabetes mellitus.

Variable events	Death event		Microvascular event		Macrovascular event	
	Hazard ratio	P	Hazard ratio	P	Hazard ratio	P
Age (years)	1.08	0.0294	1.04	0.0569	1.19	0.1988
Gender (Male/Female)	0.71	0.4607	0.59	0.1381	0.27	0.0520
Diabetes duration (years)	1.00	0.3546	1.00	0.1715	1.00	0.9016
Laboratory variables						
HbA1c (NGSP) (%)	0.83	0.3721	1.00	0.9501	0.70	0.2561
Triglycerides (mg/dl)	1.00	0.4746	1.00	0.8221	1.00	0.9713
Total cholesterol (mg/dl)	1.00	0.4048	1.00	0.1825	1.01	0.2909
LDL-cholesterol (mg/dl)	1.00	0.0864	1.00	0.0617	1.03	0.0844
HDL-cholesterol (mg/dl)	1.00	1.00	1.00	0.6874	0.97	0.3555
Serum creatinine (mg/dl)	0.92	0.8610	0.8610	0.0510	1.01	0.9949
UAER (mg/g creatinine)	1.00	0.0378	0.0378	0.0761	1.00	0.6406
Microvascular complications	1.55	0.3804	1.00	0.9980		
Macrovascular complications	5.37	0.0039	8.19	< 0.0001		
Medical treatment						
Therapy for hypertension	0.16	0.0014	0.37	0.0133	0.22	0.0938
Therapy for diabetes mellitus						
Non-insulin	2.75	0.3366	1.06	0.9140	9.44	0.1050
Insulin	0.82	0.8179	0.44	0.2787	8.52	0.1660
Therapy for dyslipidemia	1.19	0.7549	2.17	0.0372	0.42	0.3145
Therapy for hypercoagulation	2.79	0.0456	1.50	0.3294	36.8	< 0.0001
Therapy for other disease	0.56	0.3704	0.95	0.8999	2.46	0.2306

Each event was determined in obese patients with morning hypertension on the basis of home blood pressure (HBP) measured at end-point, as shown in the Table 1, which was determined by the log-rank test. The characteristics of participants related to each outcome at end-point and additional therapy, which is added to basal therapy at each end-point, were confounding factors. Blood pressure was excluded as a risk factor for each event in patients with morning hypertension using HBP. The same threshold of normotension with less than 130 mmHg of systolic blood pressure of HBP and clinic blood pressure at end-point in the text was used. The end-point was determined by the censoring date. Associated risk factors among the confounding factors were assessed using Cox proportional hazard analysis. Two-tailed values of $P < 0.05$ were defined as statistically significant.

Abbreviation: HDL: High density lipoprotein, LDL: Low density lipoprotein, NGSP: National glycohemoglobin standardization program, UAER: Urinary albumin excretion rate.

relationships between morning HBP (mmHg) at base- and end-point, and BMI (kg/m^2) were described as shown in (Figure 1A and Figure 1B). There was significant relationship between morning HBP at end-point and BMI in 400 patients with T2DM (Figure 1B).

Other variables: Means of age and duration of discovered diabetes mellitus were long (Table 1). The values of TG and UAER at basal point, and HbA1c, HDL and TG at end-point were significantly higher in the obese patients than in the non-obese patients. Therapies for other diseases were insignificantly between the non-obesity and the obesity (Table 1 and Table 3).

End-points and outcome

Primary outcome: In terms of the primary outcome, mean survey duration until end-point in obese patients was 85 ± 40 months (range, 1-120 months). Eighty one cumalative deaths in the in the patients were observed over 10 years (Table 2). The causes were

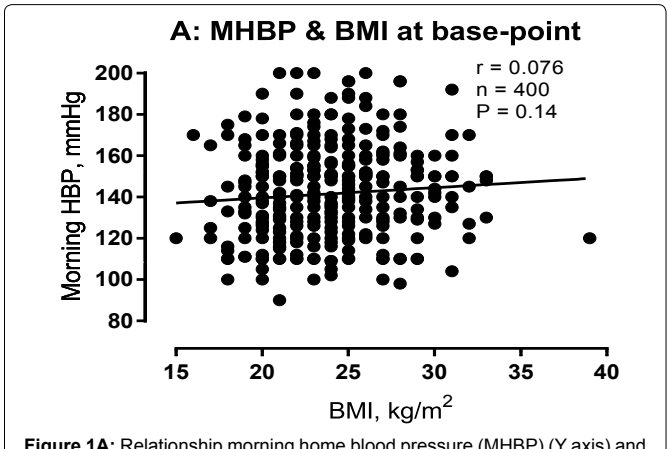

Figure 1A: Relationship morning home blood pressure (MHBP) (Y axis) and body mass index (BMI) (X-axis) measured at base-line was shown.

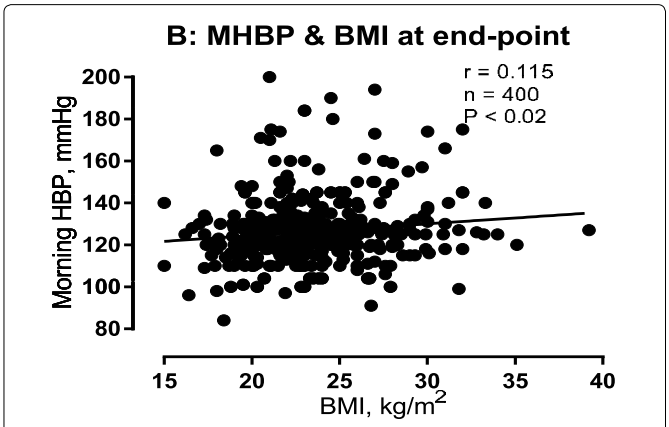

Figure 1B: Relationship morning home blood pressure (MHBP) (Y axis) and body mass index (BMI) (X-axis) measured at end-point was shown.The each relationship was calculated by Pearson method.

cancer, CVD, CHD, respiratory diseases and other diseases in 36, 18, 14, 6 and 7 patients (n = 81), respectively. Among them, 10, 9, 4 and 2 patients (n = 25) at end-point in the obese patients were due to cancer, CVD, CHD and other diseases. On the other hand, there was significant difference in events of death using the different thresholds of HBP and CBP in the obese patients (Table 4), whose incidence of HT of HBP was increased from 47 to 73 persons. Significantly more patients were receiving anti-hypertensive agents in patients using HBP with HT at end-point in comparison with those at baseline. In patients using HBP with sustained HT, 7 patients at baseline refused to use increased doses or new medicines for HT, whereas 32 patients at baseline achieved NT after the treatment. The hazard ratio in death in the obese patients using HBP at end-point was significantly higher in HT than in NT (Table 2), and value of difference was significantly ($P = 0.0024$) lower in CBP than in HBP (Table 2). Twenty one cumulative deaths in overweight patients were observed over 10 years (Table 6). The causes in 9, 7, 3, 1 and 1 patients (n = 21) in overweight patients

Table 4: Primary and secondary outcomes based on HBP# and CBP## measured at end-point in 116 obese patients with type 2 diabetes mellitus.

Outcome	Patient status: HBP* at end-point in 116 obese patients				Patient status: CBP** at end-point in 116 obese patients			
	Hypertension	Normotension	Hazard ratio	P	Hypertension	Normotension	Hazard ratio	P
	(n = 73)	(n = 43)	(95% CI)		(n = 54)	(n = 62)	(95% CI)	
Primary outcome								
Death	20	5	0.4 (0.2-1.0)	0.0500	13	11	2.4 (1.0-5.0)	0.4904
Secondary outcome								
Microvascular complications	46	25	1.4 (1.0-2.5)	0.1085	34	37	0.9 (0.5-1.7)	0.7110
Macrovascular complications	20	5	2.6 (1.0-5.1)	0.0463	13	12	1.2 (0.6-2.7)	0.5810

The obesity was defined by as the definition of the criteria of Japan Society for the Study of Obesity. Body mass Index (BMI) with ≧ 25.0 kg/m^2 was defined as obesity. The 400 patients in each group were classified as having obesity and hypertension or normotension according to values of blood pressure as recent guidelines show normotensions are less than 125 mm Hg measured in the home (HBP#) and less than 130 mmHg measured in the clinic (CBP##) at end-point, respectively. Differences in primary and secondary outcomes for events between obese patients with hypertension and normotension measured at end-point in each group were assessed using survival curves from the Kaplan-Meier method, and comparisons were analyzed using hazard ratio by the log-rank test. CI, confidence interval. Two-tailed values of P < 0.05 were defined as statistically significant.

Table 5: Primary and secondary outcomes based on HBP* and CBP** at end-point in 284 non-obese patients with type 2 diabetes mellitus.

Outcomes	Patient status: HBP* at end-point in 284 non-obese patients				Patient status: CBP** at end-point in 284 non-obese patients			
	Hypertension (n = 78)	Normotension (n = 206)	Hazard ratio (95% CI)	P	Hypertension (n = 133)	Normotension (n = 151)	Hazard ratio (95% CI)	P
Primary outcome								
Death	22	33	2.4 (1.6-5.8)	0.0008	28	27	1.2 (0.7-2.1)	0.5803
Secondary outcome								
Microvascular complications	80	22	1.8 (1.2-2.0)	0.0455	50	52	1.1 (0.8-1.7)	0.3156
Macrovascular complications	16	26	0.8 (1.6-6.9)	0.3763	38	4	4.8 (1.6-5.6)	0.0009

Characteristics of non-obese patients on HBP and CBP measured at end-point are shown in table 1. The non-obesity was defined by the criteria of Japan Society for the Study of Obesity. Body mass Index (BMI) with < 25.0 kg/m^2 was defined as non-obesity. The 400 patients in each group were classified as having non-obesity and hypertension or normotension according to values of blood pressure as same threshold of normotension with less than 130 mm Hg of systolic blood pressure measured in the home (HBP*) and in the clinic (CBP**) at end-point, respectively. Differences in primary and secondary outcomes for events between non-obese patients with hypertension or normotension measured at end-point in each group were assessed using survival curves from the Kaplan-Meier method, and comparisons were analyzed using hazard ratio by the log-rank test. CI, confidence interval. Two-tailed values of P < 0.05 were defined as statistically significant.

Table 6: Primary and secondary outcomes based on HBP* and CBP** at end-point in 96 overweight patients with type 2 diabetes mellitus.

Outcomes	Patient status: HBP* at end-point in 96 overweight patients				Patient status: CBP** at end-point in 96 overweight patients			
	Hypertension (n = 30)	Normotension (n = 66)	Hazard ratio (95% CI)	P	Hypertension (n = 42)	Normotension (n = 54)	Hazard ratio (95% CI)	P
Primary outcome								
Death	13	8	3.6 (1.7-10.5)	0.0244	12	9	1.6 (0.7-3.7)	0.2976
Secondary outcome								
Microvascular complications	21	34	2.1 (1.8-6.6)	0.0010	16	31	1.0 (0.5-1.8)	0.9496
Macrovascular complications	9	6	3.2 (1.3-11.0)	0.0184	7	8	1.1 (0.6-3.0)	0.8795

The overweight was defined by as the criteria of Japan Society for the Study of Obesity. Body mass Index (BMI) with from < 25.0 kg/m^2 to < 30 kg/m^2 was defined as overweight. The 400 patients in each group were classified as having overweight and hypertension or normotension according to values of blood pressure as same threshold with less than 130 mmHg of systolic blood pressure measured in the home (HBP*) and in the clinic (CBP**) at end-point, respectively. Differences in primary and secondary outcomes for events between overweight patients with hypertension and normotension measured at end-point in each group were assessed using survival curves from the Kaplan-Meier method, and comparisons were analyzed using hazard ratio by the log-rank test. CI, confidence interval. Two-tailed values of P < 0.05 were defined as statistically significant

were CVD, cancer, hepatic disease and respiratory disease. There were significant differences between with HT and NT using HBP in the overweight patients as the Kaplan-Meier method (Table 6).

Secondary outcomes

a. Microvascular complications: Mean survey duration until the end-point in the 116 obese patients related to microvascular complication was 85 ± 38 months (range 6 -120 months).

The complication was observed in 71 patients in the obese patients over 10 years (Table 2). An improved event was observed in 15 patients including 10 with neuropathy and 5 with nephropathy, whereas 20 patients had new or worsened complications. Forty two patients had no changes until end-point. At end-point, there were significant differences in events of microvascular complication in the obese patients using the same threshold of NT between patients with HT and NT as the Kaplan-Meier method (Table 2). There was no significant difference in the events using the different threshold at end-point in the obese patents, although whose incidence of HT of HBP was increased from 47 to 73 persons. Hazard rate was significantly (2 fold) higher in the obese patients than in non-obese patients (Table 2).Although ROC curve showed that there was no significant difference in the events between HT of and NT using the same thresholds at basal (Table 7) and end-points (Table 8) in the obese patients, the incidence of events in the obese patients had significantly higher in HT than in NT (Table 4 and Table 9). Accordingly, elevated HBP in obese patients may be related to microvascular complications.

b. Macrovascular complications: Mean survey duration until end-point related in the 116 obese patients to macrovascular complication was 38.4±30 months (range 7.2-108 months). The events were seen in 25 of the obese patients over 10 years (Table 2). Although cumulative

Table 7: ROC curve for micro-and macrovascular complications in comparison with morning HBP and CBP at basal point in 153 obese patients with type 2 diabetes mellitus.

Variable	P value
Microvascular events	0.7409
Macrovascular events	0.5202

Clinical characteristics of obese patients with type 2 diabetes mellitus on blood pressure measured at basal point were shown. The obesity was defined by the criteria using body mass index (BMI) of Japan Society for the Study of Obesity. BMI with ≧ 25.0 kg/m^2 was defined as obesity. Blood pressure using clinic blood pressure (CBP) and home blood pressure (HBP) measured once in each clinic visit and in the same morning at each clinic visit within 10 minutes after awakening in the sitting position were measured at basal point shown as the same threshold of normotension with less than 130 mmHg of systolic blood pressure measurements in morning HBP and CBP. Two tailed values of P < 0.05 were defined as statistically significant.

Abbreviation: ROC: Receiving operative characteristics

Table 8: ROC curve of death, micro- and macrovascular complications in comparison with morning HBP and CBP at end-point in 116 obese patients with type 2 diabetes mellitus.

Variable	P value
Death	0.9780
Microvascular events	0.6430
Macrovscular events	0.1889

Clinical characteristics of obese patients with type 2 diabetes mellitus on blood pressure measured at end-point were shown. The obesity was defined by the criteria using body mass index (BMI) of Japan Society for the Study of Obesity. BMI with ≧ 25.0 kg/m² was defined as obesity. Blood pressure using clinic blood pressure (CBP) and home blood pressure (HBP) measured once in each clinic visit and in the same morning at each clinic visit within 10 minutes after awakening in the sitting position were measured at end-point shown as the same threshold of normotension with less than 130 mmHg of systolic blood pressure measurements in morning HBP and CBP. Two tailed values of $P < 0.05$ were defined as statistically significant.

Abbreviation: ROC: Receiving operative characteristics

Table 9: Evaluations with morning HBP or CBP between HT and NT at end-point for death, and micro- and macrovascular events in 116 obese patients with type 2 diabetes mellitus.

Variables	HT	NT	Odds ratio (95%)	P value
Death (morning HBP)	16	9	3.4 (1.4-8.7)	0.0107
Microvascular events (morning HBP)	31	40	5.3 (2.4-12.0)	0.001
Macrovascular events (morning HBP)	18		4 3.4 (1.4-8.7)	0.0107
Death (CBP)	17	8	2.7 (1.1-6.9)	0.0425
Microvascular events (CBP)	34	37	0.9 (0.4-1.9)	0.8491
Macrovscular events (CBP)	13	12	1.2 (0.5-2.8)	0.8231

Clinical characteristics of obese patients with type 2 diabetes mellitus on blood pressure measured at end-point were shown. The obesity was defined by the criteria using body mass index (BMI) of Japan Society for the Study of Obesity. BMI with ≧ 25.0 kg/m² was defined as obesity. Blood pressure using clinic blood pressure (CBP) and home blood pressure (HBP) measured once in each clinic visit and in the same morning at each clinic visit within 10 minutes after awakening in the sitting position were measured at end-point as the same threshold shown as normotension with less than 130 mmHg of systolic blood pressure measurements in morning HBP and CBP. Two tailed values of $P < 0.05$ were defined as statistically significant.

Abbreviation: HT: Hypertension, NT: Normotension

events of macrovascular events were insignificant ($P = 0.059$) between non-obese patients and obese patients, the incidence in the obese patients had a tendency of high compared with that in the non-obese patients. Among them in the obese patients, no changes were shown in 12 patients and new or worsened events were shown in 14 patients. Events in the obese patients using HBP was also significantly higher in sustained HT than in sustained NT as the Kaplan-Meier method. Further, events based on HBP using the different threshold in the obese patients were significantly higher in HT than in NT (Table 4). In addition, although ROC curves for the events in HBP at base-and end-points using the same thresholds in the obese patients were not significantly different (Table 7 and Table 8), the events in HBP at base-and end-points using the same thresholds were also significantly higher in HT than in NT (Table 9 and Table 10).The hazard rate in the obese patient in HBP using the same thresholds of NT was significantly (3 fold) higher in HT than in NT (Table 2). Accordingly, obese patients with elevated of HBP may be related to macrovascular complications

Table 10: Evaluations with morning HBP or CBP between HT and NT at basal point for micro- and macrovascular events in 153 obese patients with type 2 diabetes mellitus.

Variables	HT	NT	Odds ratio (95%)	P value
Microvascular events (Morning HBP)	94	10	6.0 (2.5-14.2)	< 0.0001
Macrovascular events (Morning HBP)	40	3	4 3 (1.2-15.2)	0.0139
Microvascular events (CBP)	93	9	6.7 (2.7-16.2)	< 0.0001
Macrovscular events (CBP)	32	11	0.8 (0.3-1.8)	0.5321

Clinical characteristics of obese patients with type 2 diabetes mellitus on blood pressure measured at basal point were shown. The obesity was defined by the criteria using of body mass index (BMI) of Japan Society for the Study of Obesity. BMI with ≧ 25.0 kg/m² was defined as obesity. Blood pressure using clinic blood pressure (CBP) and home blood pressure (HBP) measured once in each clinic visit and in the same morning at each clinic visit within 10 minutes after awakening in the sitting position were measured at basal point as shown as the same threshold of normotension with less than 130 mmHg of systolic blood pressure measurements in morning HBP and CBP. Two tailed values of $P < 0.05$ were defined as statistically significant.

Abbreviation: HT: Hypertension, NT: Normotension.

Risk factor assessment for outcomes

Death, age, UAER, macrovascular complications and therapy for hyper coagulation or HT using HBP and the same threshold of BP were significant risk-factors in the obese patients, although the hazard rate of therapy for HT was less than 1.0 (Table 3). Events of micro- and macro vascular complications and therapy for dyslipidemia or HT were also significant risk-factors in the obese patients (Table 3), although hazard rate of therapy for HT was also less than 1.0.

Discussion

Ages in patients with non-obesity and obesity were old. Subsequently, many patients had HT [4]. Recent guidelines have recommended that BP of threshold for HBP should be lower by 5-10 mmHg than that for CBP [13-15]. In this study, the same threshold of NT for CBP and HBP groups were used based on guidelines in place when this study began [12]. Nevertheless, cumulative events of death were significantly higher in the obese patients than in the non-obese patients.

Cumulative events of microvascular complications were also significantly higher in the obese patients than in the non-obese patients, and using HBP, there was significantly higher in HT than in NT, while no significant difference using CBP was seen. Cumulative events of macrovascular complications in the obese patients using HBP was significantly higher in HT than NT, although no significant difference using CBP at end-point was seen. This study also showed that the obese patients at base-point had high TG and increased UAER compared with the non-obese patients. The findings are consistent with finding previously reported [4-6,9-22].Furthermore, it demonstrated first that incidences of dead and cumulative vascular events in patients with HT using HBP at end-point were higher in obesity than in non-obesity. In the overweight patients according to guideline of the U.S.A. and the Europe [7], there were significantly more differences in micro- and macrovascular events using the same thresholds at end-point in HT than in NT. Therefore, although definition of obese is different between Japanese and non-Japanese patients with T2DM [7], the finding may be given to non-Japanese patients with T2DM.The significant relationship between morning HBP at end-point and BMI was supported this view.

Death and cumulative event of microvascular complications were related to occurring events of macrovascular disturbances and were decreased by therapy for HT of HBP and therapy treated with anti-coagulation in the obese patients. Hazard rates of primary and secondary outcomes in the obese patients using HBP were higher in HT than in NT. Measurement HBP has no gratification in not only patients also staffs of medical facilities, because that it has a nuisance or a troublesome [23-26]. However, it is demonstrated that measurement of HBP in obese patients with T2DM is necessary as this study.

All findings indicated that incidences of death and cumulative events of micro-and macrovascular complications were significantly higher in obesity than in non-obesity, and those in the obese patients were strongly related to HT of HBP and were similar to results of the Ohasama study [18 ,19], supporting the view that HBP in the obese patients has a strongly prognostic value compared in the non-obese patients. Based on the results of the present study, obesity with HT of HBP may be added to the list of risk factors in patients with T2DM [5,6].

Limitations

First, numbers of the non-obese and the obese patients, and events occurring over 10 years were heterogeneous and small, respectively. Therefore, we were unable to survey outcomes and compare differences among groups of patients with HT and NT of CBP or HBP at baseline as a cohort study, which would have provided clinically valuable information.

Second, there was no evening or 24-hour BP measurement. We classified patients into HT or NT groups based on CBP and HBP at baseline and end-point, and compared differences in cumulative events between these groups. These patients' classifications obviously overlapped.

Third, for ethical reasons, most patients received treatment with antihypertensive agents and other medications during follow-up. Conventionally, antihypertensive drugs are prescribed based on CBP values, but currently, we prescribe those drugs at bedtime based on values of morning HBP [3]. However, some patients refused dosage increases or changes in medications for HT identified based on values of morning HBP. Reasons for refusal were not due to high costs or side effects of medication, but rather to patients' and physicians' lack of acceptance of HBP values for medication adjustments. In addition, some patients may be prescribed both morning and evening doses for antihypertensive agents. If a patient takes the evening dose, the morning HBP may be controlled, but during the day, as that dose wears off, BP levels may rise again. However, we did not have BP readings based on ambulatory blood pressure monitoring. Accordingly, we were unable to examine outcomes without changing treatment from baseline over 10 years to determine the influence of these drugs. Therefore, it can be argued that it is not appropriate to classify patients who have been taking antihypertensive drugs into groups with HT or NT.

Fourth, prognostic values of CBP and HBP should be assessed as not only categorical data but also continuous data. The analysis using continuous variables may give more significant meaning, but in this study, BP as a continuous variable showed high fluctuations and the numbers of participants was small.

Conclusion

This prospective study of patients with T2DM for 10 years demonstrated that elevated morning HBP measured is significantly predictive death, and events of micro- and macrovascular complications in obese patients than in non-obese patients, suggesting that elevated HBP in patients with T2DM, in particular obese patients may be needed to decrease for preventing death, and micro and macrovascular complications. .

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Reference

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