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ORIGINAL ARTICLE

Home-measured heart rate is associated with albuminuria in patients with type 2 diabetes mellitus: a *post-hoc* analysis of a cross-sectional multicenter study

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Epidemiological studies have shown that elevated heart rate (HR) is associated with an increased risk of diabetic nephropathy, as well as cardiovascular events and mortality, in patients with type 2 diabetes mellitus. Recently, the advantages of the self-measurement of blood pressure (BP) at home have been recognized. The aim of this study was to investigate the relationship between home-measured HR and albuminuria in patients with type 2 diabetes mellitus. We designed a cross-sectional multicenter analysis of 1245 patients with type 2 diabetes mellitus. We investigated the relationship between the logarithm of urinary albumin excretion (log UAE) and home-measured HR or other factors that may be related to nephropathy using univariate and multivariate analyses. Multivariate linear regression analysis indicated that age, duration of diabetes mellitus, morning HR ($\beta = 0.131$, $P < 0.001$), morning systolic BP ($\beta = 0.311$, $P < 0.001$), hemoglobin A_{1C}, triglycerides, daily consumption of alcohol, use of angiotensin II receptor blockers and use of beta-blockers were independently associated with the log UAE. Multivariate logistic regression analysis indicated that the odds ratio (95% confidence interval) associated with 1 beat per min and 1 mm Hg increases in the morning HR and morning systolic BP for albuminuria were 1.024 ((1.008–1.040), $P = 0.004$) and 1.039 ((1.029–1.048), $P < 0.001$), respectively. In conclusion, home-measured HR was significantly associated with albuminuria independent of the known risk factors for nephropathy, including home-measured systolic BP, in patients with type 2 diabetes mellitus.

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Keywords: diabetic nephropathy; home-measured heart rate; multicenter study

INTRODUCTION

Albuminuria is an indicator of diabetic nephropathy, which is a microvascular dysfunction, and a well-established predictor of poor cardiovascular outcome in patients with diabetes mellitus.[1,2] It is crucial for patients with diabetes mellitus to prevent the development of diabetic nephropathy because it is currently the leading cause of end-stage renal disease.

Several epidemiological studies have shown that elevated heart rate (HR) is associated with an increased risk of mortality and cardiovascular events in patients with diabetes mellitus,[3] as well as in the general population,[4,5] in those with hypertension[6,7] and in those with cardiovascular disease.[8–12] Moreover, it was reported that patients with type 2 diabetes mellitus who have a higher resting HR experience a greater incidence of new-onset or progressive nephropathy in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study.[13] In these studies, HR was mainly measured in outpatient clinics.

Recently, the usefulness of the self-measurement of blood pressure (BP) at home (home BP) has been recognized. Home BP was shown to have better predictive power with respect to target organ damage relative to that of clinic BP,[14–16] as home BP is not affected by the environmental influences of the clinic, such as the so-called 'white-coat phenomenon',[17–19] and facilitates obtaining multiple measurements over a long period of time. Similar advantages would also apply to the self-measurement of HR at home (home HR), as assessed by a device used for home BP measurement. The purpose of

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this study was to evaluate, for the first time, the relationship between home HR and albuminuria in patients with type 2 diabetes mellitus.

METHODS

Patients

Home BP and home HR measurements were collected in patients with type 2 diabetes mellitus who had regularly attended the diabetes outpatient clinic at the Hospital of Kyoto Prefectural University of Medicine or one of the other four general hospitals, all of which are located in the Kansai area in Japan. We sequentially recruited 1292 type 2 diabetic patients who visited the facilities between March 2008 and October 2012. The winter season was not included to avoid the variations in BP caused by the cold weather. There was no BP-level criterion for study inclusion. Of the 1292 patients with type 2 diabetes mellitus, we excluded patients who failed to adequately measure their home BP ($n=36$) and those who presented advanced renal dysfunction (serum creatinine equal to or more than 2.0 mg dl^{-1}; $n=11$). Consequently, 1245 patients comprised the study population (693 male and 552 female). The diagnosis of type 2 diabetes mellitus was based on the American Diabetes Association criteria.[20]

Study design

We designed a cross-sectional multicenter study in general hospitals. We investigated the relationship between the logarithm of urinary albumin excretion (log UAE) and home HR or other factors that may be related to nephropathy using a linear regression analysis. We then evaluated whether home HR was independently associated with log UAE using multivariate linear regression analysis after adjusting for the variables, including the significant variables from a linear regression analysis and those known to be risk factors for nephropathy. Furthermore, we evaluated multivariate adjusted odds ratios for albuminuria, which was defined as UAE equal to or more than 30 mg per g of creatinine (mg g^{-1} Cr), using logistic regression models. All procedures of the present study were approved by the local research ethics committee and conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from all patients.

Home BP and HR measurements

Patients were instructed to perform triplicate morning and evening BP and HR measurements for 14 consecutive days. The mean of three measurements in the morning and in the evening for 14 consecutive days were taken as the home BP and HR in this study. The morning measurements of BP and HR were made within 1 h of awakening, before eating breakfast or taking any drugs, with the patient seated and rested for at least 5 min.[19] The evening measurements of BP and HR were obtained in a similar manner just before going to bed. The cuff was placed around the non-dominant arm, and the position of the cuff was maintained at the level of the heart. Home BP and HR measurements were taken using HEM-70801C automatic devices (Omron Healthcare, Kyoto, Japan), which use the cuff-oscillometric method to generate a digital display of systolic/diastolic BP and HR values. HEM-70801C employs components and a BP determining algorithm that are identical to those of another device, HEM-705IT, which was previously validated and satisfied the criteria of the British Hypertension Society protocol.[21] Clinical BP and HR were taken as the mean of three readings using the HEM-70801C while we rented the device. We used the HR values displayed on the electronic BP monitor, which were automatically calculated as follows: HR (beats per min) = (number of pulse interval) × 60/(averaged pulse interval). The manufacturer of the monitor guarantees its accuracy, with a reading error of ± 5% at the maximum.

Data collection

Blood samples were taken in the morning for biochemical measurements. Hemoglobin A_{1C}, serum lipid profile (total cholesterol, low-density lipoprotein cholesterol, triglycerides, and high-density lipoprotein cholesterol) and other biochemical data were determined using standard laboratory measurements. Hemoglobin A_{1C} was expressed as National Glycohemoglobin Standardization Program units. Data, including age, duration of diabetes, smoking and alcohol consumption status and antihypertensive medication, were assessed concurrently with the BP and HR measurements. Retinopathy was assessed from chart reviews and was graded as follows: no diabetic retinopathy, simple diabetic retinopathy and proliferative diabetic retinopathy. Nephropathy was graded as follows: normoalbuminuria, UAE less than 30 mg g^{-1} Cr; microalbuminuria, 30–300 mg g^{-1} Cr; or macroalbuminuria, more than 300 mg g^{-1} Cr. Neuropathy was defined by the diagnostic criteria for diabetic neuropathy proposed by the Diagnostic Neuropathy Study Group.[22] Briefly, in the absence of peripheral neuropathies other than diabetic neuropathy in diabetic patients, diabetic neuropathy is diagnosed by two or more abnormalities among three neurological examination items: sensory symptoms, decreased or absent ankle reflex (bilateral) and decreased vibratory sensation on bilateral medial malleoli evaluated using a c128 Hz tuning fork. A macrovascular complication was defined as the presence of previous cardiovascular disease, cerebrovascular disease or arteriosclerosis obliterans based on the clinical history or physical examination. Smoking status (current, past or never) and alcohol consumption status (daily, social or never) were assessed during an interview.

Statistical analysis

Values were expressed as the means ± s.d. for continuous variables and as numbers for categorical variables. Because UAE showed a skewed distribution, a logarithmic transformation was carried out before performing statistical analysis. Univariate and multivariate linear regression analyses were used to compare the relationships between log UAE and factors that appeared as significant variables in a linear regression analysis and those known to be risk factors for nephropathy (age, sex, duration of diabetes mellitus, body mass index, home HR, home systolic BP, hemoglobin A_{1C}, total cholesterol, triglycerides, smoking status, alcohol consumption status, use of angiotensin II receptor blockers (ARBs), use of angiotensin-converting enzyme inhibitors (ACE-Is), use of calcium channel blockers, use of diuretics, use of beta-blockers and use of alpha-blockers). Multivariate logistic analyses were used to determine the contribution of the variables mentioned above to albuminuria. We calculated odds ratios and 95% confidence intervals to describe the changes in risk associated with 1-unit increase in each continuous variable. Two-tailed values of $P<0.05$ were considered to indicate statistical significance. All statistical analyses were performed using SPSS version 11.0 J (SPSS, Chicago, IL, USA).

RESULTS

Clinical characteristics of the patients in this study are shown in Table 1. A total of 1245 patients were included in this study, and 55.7% of the patients were male. The mean age and hemoglobin A_{1C} were 65.5 ± 9.8 years and 7.2 ± 1.1%, respectively. A total of 721 patients (57.9%) were treated with antihypertensive drugs. Of these patients, 432 patients (59.9%) were receiving calcium channel blockers (CCBs), 520 (72.1%) were receiving ARBs, 94 (13.1%) were receiving ACE-I, 106 (14.7%) were receiving diuretics, 93 (12.9%) were receiving beta-blockers and 27 (3.7%) were receiving alpha-blockers. The mean home HR values were 68.8 ± 9.7 beats per min in the morning and 72.4 ± 10.1 beats per min in the evening, whereas the mean home systolic/diastolic BP values were 135.6 ± 18.1/74.9 ± 10.6 mm Hg in the morning and 130.9 ± 17.5/69.8 ± 10.0 mm Hg in the evening.

In the univariate analyses, age ($\gamma=0.162$, $P<0.001$), duration of diabetes mellitus ($\gamma=0.194$, $P<0.001$), body mass index ($\gamma=0.059$, $P=0.048$), morning HR ($\gamma=0.102$, $P<0.001$), morning systolic BP ($\gamma=0.378$, $P<0.001$), evening HR ($\gamma=0.091$, $P=0.002$), evening systolic BP ($\gamma=0.326$, $P<0.001$) and triglycerides ($\gamma=0.083$, $P=0.005$) were associated with the log UAE (Table 2).

Multivariate linear regression analyses indicated that age, duration of diabetes mellitus, morning HR, morning systolic BP, hemoglobin A_{1C}, triglycerides, daily consumption of alcohol, use of ARBs and use of beta-blockers were independently associated with log UAE. Furthermore, age, duration of diabetes mellitus, evening HR, evening systolic BP, hemoglobin A_{1C}, use of ARBs, use of CCBs and

Table 1 Clinical characteristics of patients

Characteristic	
N	1245
Sex (male/female)	693/552
Age (years)	65.5 ± 9.8
Duration of diabetes mellitus (years)	12.3 ± 9.6
Body mass index (kg m^{-2})	23.8 ± 4.0
Clinic heart rate (beats per min)	73.7 ± 11.9
Clinic systolic blood pressure (mm Hg)	139.8 ± 19.2
Clinic diastolic blood pressure (mm Hg)	77.3 ± 11.2
Hemoglobin A_{1C} (% (mmol mol^{-1}))	7.2 ± 1.0 (55 ± 13)
Total cholesterol (mmol l^{-1})	4.91 ± 0.84
Triglycerides (mmol l^{-1})	1.55 ± 0.97
High-density lipoprotein cholesterol (mmol l^{-1})	1.46 ± 0.41
Creatinine (mg dl^{-1})	0.78 ± 0.24
Smoking status (current/past/never)	248/342/655
Alcohol consumption status (everyday/social/never)	314/263/668
Nephropathy (normo-/micro-/macroalbuminuria)	703/431/111
Retinopathy (NDR/SDR/PDR)	890/217/138
Neuropathy (−/+)	814/431
Macrovascular complication (−/+)	922/323
Hypoglycemic treatment (diet/OHA/insulin/GLP-1)	168/838/280/3
Antihypertensive medication (−/+)	524/721
CCB/ARB/ACE inhibitors/diuretics/beta-blockers/alpha-blockers	432/520/94/106/93/27
Morning heart rate (beats per min)	68.8 ± 9.7
Evening heart rate (beats per min)	72.4 ± 10.1
Morning systolic blood pressure (mm Hg)	135.6 ± 18.1
Evening systolic blood pressure (mm Hg)	130.9 ± 17.5
Morning diastolic blood pressure (mm Hg)	74.9 ± 10.6
Evening diastolic blood pressure (mm Hg)	69.8 ± 10.0

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blockers; GLP-1, glucagon-like peptide-1receptor agonist; NDR, no diabetic retinopathy; OHA, oral hypoglycemic agent; PDR, proliferative diabetic retinopathy; SDR, simple diabetic retinopathy.
Data are means ± s.d. or number.

Table 2 Multiple regression analysis on logarithm of urinary albumin excretion in patients with type 2 diabetes mellitus

	Multivariate[a]			
	Morning		*Evening*	
	β	P-*value*	β	P-*value*
Age (years)	0.074	0.029	0.086	0.013
Sex (male = 1, female = 0)	0.010	0.777	0.016	0.669
Duration of diabetes mellitus (years)	0.148	<0.001	0.149	<0.001
Body mass index (kg m^{-2})	0.014	0.670	0.009	0.776
Morning heart rate (beats per min)	0.131	<0.001	—	—
Evening heart rate (beats per min)	—	—	0.124	<0.001
Morning systolic blood pressure (mm Hg)	0.311	<0.001	—	—
Evening systolic blood pressure (mm Hg)	—	—	0.257	<0.001
Hemoglobin A_{1C} (%)	0.063	0.038	0.066	0.027
Total cholesterol (mmol l^{-1})	−0.002	0.942	−0.008	0.801
Triglycerides (mmol l^{-1})	0.063	0.038	0.061	0.051
Smoking status				
None *vs.* past	0.052	0.151	0.036	0.333
None *vs.* current	0.054	0.112	0.035	0.325
Alcohol consumption status				
Never *vs.* social	−0.011	0.731	−0.008	0.796
Never *vs.* everyday	−0.087	0.011	−0.058	0.104
Angiotensin II receptor blockers (no = 0, yes = 1)	0.093	0.006	0.110	0.002
Angiotensin-converting enzyme inhibitors (no = 0, yes = 1)	0.038	0.220	0.049	0.122
Calcium channel blockers (no = 0, yes = 1)	0.067	0.053	0.086	0.014
Diuretics (no = 0, yes = 1)	0.053	0.080	0.046	0.139
Beta-blockers (no = 0, yes = 1)	0.080	0.010	0.090	0.005
Alpha-blockers (no = 0, yes = 1)	−0.008	0.784	−0.029	0.331

β indicates multiple linear regression coefficient.
[a]Adjusted for all variables in this table.

use of beta-blockers were independently associated with the log UAE (Table 2).

The odds ratios (95% confidence interval) for albuminuria, which express the risk associated with a 1-unit increase in each continuous variable, were 1.029 ((1.013–1.046) $P<0.001$) for the duration of diabetes mellitus, 1.024 ((1.008–1.040), $P=0.004$) for the morning HR, 1.039 ((1.029–1.048), $P<0.001$) for the morning systolic BP, 1.002 ((1.000–1.004), $P=0.028$) for triglycerides, 0.581 ((0.388–0.870), $P=0.008$) for daily alcohol consumption and 1.644 ((1.156–2.339), $P=0.006$) for the use of CCB. Multivariate logistic regression analyses revealed that the odds ratios (95% confidence interval) for albuminuria were the following: 1.029 ((1.013–1.045), $P<0.001$) for duration of diabetes mellitus, 1.027 (1.011–1.044) for evening HR, 1.035 ((1.026–1.045], $P<0.001$) for evening systolic BP and 1.778 ((1.249–2.532), $P=0.001$) for the use of CCB (Table 3).

DISCUSSION

Principal findings

This large-scale cross-sectional study of patients with type 2 diabetes mellitus revealed, for the first time, that home-measured HR was significantly associated with albuminuria independent of the known risk factors for nephropathy, such as age, sex, duration of diabetes mellitus, body mass index, systolic BP and serum lipid profile.

Interpretations

The advantages of home BP are recognized because home BP, which has better reproducibility due to the absence of environmental influences such as the so-called white coat effect,[17–19] was shown to have a stronger relationship with target organ damage in several population-based studies and prospective clinical studies.[14–16,23] These advantages presumably also apply to the self-measurement of home HR, as assessed by a device used for home BP measurement. The Ohasama study, a well-known large-scale longitudinal observational study of ambulatory BP monitoring and home BP measurement in Japan,[14–16] demonstrated that home-measured resting HR was able to predict cardiovascular disease mortality.

Therefore, we investigated the relationship between home HR and albuminuria, which is an indicator of diabetic nephropathy and a well-established predictor of poor cardiovascular outcome in patients with diabetes mellitus.[1,2] We then revealed, for the first time, that home HR was significantly associated with albuminuria independent of the known risk factors for nephropathy in patients with type 2 diabetes mellitus.

Several possibilities for the relationship between HR and target organ damage are postulated from the results of animal studies and

Table 3 Multivariate adjusted odds ratios for albuminuria in patients with type 2 diabetes mellitus

	Morning		*Evening*	
	Odds ratio (95% CI)	P-*value*	*Odds ratio (95% CI)*	P-*value*
Age	1.017 (1.000–1.035)	0.054	1.020 (1.003–1.038)	0.024
Sex (male = 1, female = 0)	1.221 (0.839–1.777)	0.296	1.224 (0.840–1.784)	0.293
Duration of diabetes mellitus	1.029 (1.013–1.046)	<0.001	1.029 (1.013–1.045)	<0.001
Body mass index	0.995 (0.954–1.037)	0.797	0.996 (0.954–1.040)	0.858
Morning heart rate	1.024 (1.008–1.040)	0.004	—	—
Evening heart rate	—	—	1.027 (1.011–1.044)	0.001
Morning systolic blood pressure	1.039 (1.029–1.048)	<0.001	—	—
Evening systolic blood pressure	—	—	1.035 (1.026–1.045)	<0.001
Hemoglobin A_{1C}	1.036 (0.984–1.092)	0. 178	1.033 (0.983–1.086)	0.196
Total cholesterol	0.996 (0.991–1.001)	0.087	0.995 (0.991–1.000)	0.056
Triglycerides	1.002 (1.000–1.004)	0.028	1.002 (1.000–1.003)	0.051
Smoking status				
None *vs.* past	1.388 (0.929–2.076)	0.110	1.289 (0.859–1.934)	0.220
None *vs.* current	1.323 (0.865–2.022)	0.197	1.170 (0.763–1.794)	0.471
Alcohol consumption status				
Never *vs.* social	1.002 (0.678–1.482)	0.991	1.021 (0.688–1.513)	0.919
Never *vs.* everyday	0.581 (0.388–0.870)	0.008	0.696 (0.463–1.046)	0.081
Angiotensin II receptor blockers (no = 0, yes = 1)	1.280 (0.910–1.800)	0.156	1.385 (0.985–1.947)	0.061
Angiotensin-converting enzyme inhibitors (no = 0, yes = 1)	1.187 (0.662–2.126)	0.566	1.245 (0.693–2.236)	0.463
Calcium channel blockers (no = 0, yes = 1)	1.644 (1.156–2.339)	0.006	1.778 (1.249–2.532)	0.001
Diuretics (no = 0, yes = 1)	1.061 (0.628–1.794)	0.825	1.014 (0.598–1.719)	0.959
Beta-blockers (no = 0, yes = 1)	1.638 (0.890–3.014)	0.113	1.807 (0.981–3.325)	0.057
Alpha-blockers (no = 0, yes = 1)	0.679 (0.254–1.815)	0.440	0.467 (0.169–1.294)	0.143

Abbreviation: CI, confidence interval.
β indicates multiple linear regression coefficient.
Adjusted for all variables in this table. Odds ratios given with 95% CIs express the risk associated with 1-unit increase in each continuous variable.

human studies. Experimental studies in animal models of atherosclerosis demonstrated that elevated HR is associated with enhanced experimental atherosclerotic plaque formation.[24] It was also reported that monkeys with higher HR had more extensive coronary atherosclerosis than those with lower HR.[25] An elevated HR increases the magnitude and frequency of the tensile stress inflicted on the arterial wall, prolongs the exposure of the coronary endothelium to oscillatory shear stress and intensifies the periodically changing geometry of the coronary arteries, which in turn affects the local hemodynamic environment.[26] All these processes induce structural and functional changes in the endothelial cells and modulate an atherogenic microenvironment, which act in conjunction with systemic risk factors (such as poor glycemic control) to promote atherosclerosis in atherosclerosis-prone regions.[26] Moreover, patients with type 2 diabetes mellitus who present a higher resting HR in clinical settings are more likely to present microalbuminuria and also experience a greater incidence of new-onset or progressive nephropathy according to the ADVANCE study.[13] It has been suggested that an elevated HR might promote microalbuminuria because of increased exposure of the glomerulus to arterial pressure waves.[27]

HR reduction with beta-blockers is associated with improved outcomes in patients with chronic heart failure.[28] In the SHIFT study, ivabradine substantially and significantly reduced the major risks associated with heart failure when added to a guideline- and evidence-based treatment.[29] However, whether a HR-lowering strategy results in a benefit in terms of renal outcomes has not been ascertained.

According to multivariate logistic regression analyses, the use of ACE-I or ARB was not associated with the existence of albuminuria, and the use of CCB was positively associated with it. These results might be partially explained as a consequence of reverse causality because of the cross-sectional nature of the study. Morning systolic BP was significantly higher in patients with antihypertensive medication than in those without antihypertensive medication (138.7 ± 17.4 *vs.* 131.4 ± 18.1 mm Hg, $P < 0.001$), and log UAE was significantly higher in patients with antihypertensive medication than in those without antihypertensive medication (1.61 ± 0.67 *vs.* 1.33 ± 0.59, $P < 0.001$). In other words, we prescribed antihypertensive medication to patients with hypertension and albuminuria. The use of ACE-I or ARB was not associated with the existence of albuminuria because these drugs have renoprotective effects;[30] however, the use of CCB was positively associated with the existence of albuminuria because its renoprotective effects are not as great compared with those of ACE-I or ARB, we speculate.

The strengths of the present study include the large number of patients with type 2 diabetes mellitus who measured their home HR and home BP, the fact that we used a device equipped with a memory to store readings rather than trusting patient logbooks, which can show poor adherence,[31] and the fact that home HR and home BP measurements were collected over a relatively long consecutive period.

The limitation of this study is its cross-sectional nature, as the cause–effect relationship between home-measured HR and albuminuria cannot be addressed clearly as a result.

In conclusion, the present study revealed, for the first time, that home-measured HR was significantly associated with albuminuria,

independent of the known risk factors for nephropathy in patients with type 2 diabetes mellitus, suggesting that a reduction of the home HR may have the potential to prevent the development of diabetic nephropathy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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