ORIGINAL ARTICLE

Blood pressure circadian rhythms and adverse outcomes in type 2 diabetes patients diagnosed with orthostatic hypotension

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ABSTRACT

Aims/Introduction: Patients with diabetes frequently develop orthostatic hypotension (OH). The present study was designed to examine the relationship of blood pressure (BP) circadian rhythms and outcomes in diabetes with OH.

Materials and Methods: In the present study, 173 inpatients with type 2 diabetes were enrolled. Patients were divided into an OH group and a non-OH group according to the BP changes detected in the supine and standing position. Then, 24-h ambulatory BP was monitored. Patients were followed up for an average of 45 ± 10 months post-discharge. Outcomes – death and major adverse cardiac and cerebrovascular events, including heart failure, myocardial infarction and stroke – were recorded.

Results: There were 61 patients (35.26%) in the OH group and 112 patients (64.74%) in the non-OH group. In the OH group, the night-time systolic BP and night-time diastolic BP were higher, the blood BP rhythms were predominantly of the riser type (67.21%). OH was as an independent marker of riser type circadian rhythm (adjusted odds ratio 4.532, 95% confidence interval 2.579–7.966). In the OH group, the incidence rates of mortality, and major adverse cardiac and cerebrovascular events were increased significantly compared with those in the non-OH group (11.48 vs 2.68%, $P = 0.014$; 37.70 vs 8.93%, $P < 0.01$).

Conclusions: In patients who had type 2 diabetes diagnosed with OH, the BP circadian rhythm usually showed riser patterns, and they had increased rates of mortality, and major adverse cardiac and cerebrovascular events.

INTRODUCTION

Diabetes and orthostatic hypotension (OH) are companions[1]. OH is a cardiovascular disorder that is diagnosed when blood pressure (BP) decreases significantly when the patient stands up from the supine or sitting position. OH can provoke signs and symptoms of cerebral hypoperfusion, such as dizziness, weakness, fatigue, light headedness, nausea, 'coat-hanger' pain and syncope. OH can also be asymptomatic if the rate of decrease of BP is low enough as the patient changes position. OH can be a manifestation of diabetic autonomic dysfunction, and can lead to an increased risk of syncope, cardiovascular diseases and severe adverse outcomes[2–4].

It is thus important to diagnose and treat OH early on, so as to avoid major adverse events. Further studies on diabetes patients with OH are required to characterize this disorder, because patients with OH are generally asymptomatic. It is known that BP follows a circadian pattern, as modulated by autonomic nervous system activity. Ambulatory BP monitoring is a non-invasive modality that can be used over a 24-h period to characterize circadian variations (dipper, non-dipper, extreme dipper and riser). A decline in nocturnal BP of 10–20% is considered normal, and is defined as a dipper pattern. Non-dipper, riser and extreme-dipper BP patterns are considered to be abnormal[5,6]. This method is able to evaluate whether the loss of the expected BP circadian rhythm is associated with cardiovascular events, morbidity and mortality[7,8]. We used 24-h ambulatory BP monitoring in the present study to determine

whether any of these three key changes in circadian BP patterns are subsequently associated with an increased risk of adverse cardiac and cerebrovascular events, and mortality during long-term follow up.

METHODS

Study design and participants

The study was carried out in the Department of Internal Medicine, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China. The protocol was reviewed and approved by the Medical Ethics Committee of the Beijing Chaoyang Hospital, Capital Medical University. All persons provided informed consent to participate after they were informed of the risks associated with the research verbally and in writing. Inclusion criteria included male or female inpatients, aged >18 years, with type 2 diabetes according to the American Diabetes Association criteria[9]. Patients who could lie down for more than 5 min and then stand up by themselves for 3 min were selected. Exclusion criteria included pregnancy, New York Heart Association functional class III/IV, hypovolemia, hypoproteinemia, anemia and sleep apnea syndrome.

Data collection and follow up

A total of 173 participants were recruited, and their brachial BP levels were measured in both the supine and standing position for each. For the supine BP, the cuffs were placed on the participants' upper right arms and measurements were taken twice at an interval of 1–2 min after at least 5 min in the recumbent position. An average of the systolic BPs (SBP) as well as that of the diastolic BPs (DBP) was deemed as the supine BP. The participants were then asked to stand up, and after 1–3 min for equilibration, the BP was again taken twice, with the average values being deemed as the standing BP. SBP and DBP were measured manually using a mercury sphygmomanometer by experienced doctors. At the same time, heart rate was recorded too. The diagnostic criteria for OH were according to the consensus statement of 2011[10]. Specifically, this diagnosis required a sustained reduction of SBP of ≥20 mmHg within 3 min after the participants' change to standing position, and (or) a DBP decrease ≥10 mmHg. With regard to the participants with supine hypertension, a SBP decrease ≥30 mmHg was required to diagnose OH. The enrolled participants were divided into an OH group and a non-OH group based on the aforementioned BP measurements and OH criteria.

Each participant's hospitalization data were recorded as per protocol. During the physical examination on admission, the height and weight were recorded, and body mass index (BMI) was calculated: BMI = bodyweight (kg) / height (m)^2. The medical history, including any hypertension, diabetes or coronary heart disease, together with the use of any antihypertensive drugs, was recorded. All participants underwent 24-h ambulatory BP monitoring (using a Model 90217 monitor; SpaceLabs Healthcare, Hawthorne, California, USA) on 1–3 days

after patients' admission. Participants were commonly instructed to begin bed rest or try to sleep before midnight and to rise after morning. During the monitoring period, BP was measured at 30-min intervals during the daytime, and at 60-min intervals during the night-time. Night-time (for the 60-min BP monitoring interval) was defined as from the time patients went to bed until the time each got out of bed in the morning, and the daytime interval (for the 30-min BP measurements) as the rest of the day[11]. The 24-h BP changes could be divided into four patterns on the basis of the daytime and night-time BP: dipper, non-dipper, extreme dipper and riser (reverse or invert dipper). The normal decline in nocturnal BP by 10–20% is defined as the dipper pattern. Non-dippers and extreme dippers are defined as those with a night-time BP reduction of <10 or >20% of daytime BP, respectively. Risers have night-time BP levels that are higher than daytime levels[5,6].

All enrolled participants were followed up through telephone interviews until the end of the study on 5 April 2016, death or emigration. The primary outcome was death. Any mortality data (whether the person died, and the date and cause of death) were registered. Additionally, the number of major adverse cardiac and cerebrovascular events (MACCE), including heart failure, myocardial infarction and stroke, were recorded and analyzed.

Statistical analysis

Sample size estimation assumed, the prevalence of OH in patients with type 2 diabetes is approximately one-third[12], mortality approaching 70% and a hazard ratio of 2.0 for the OH population vs the non-OH population[1,13]. Thus, 93 patients would be required ($\alpha = 0.05$, $\beta = 0.2$; two-sided contrast). Considered a loss to follow-up rate of 20%, the sample size was increased to 112.

SPSS statistics 18.0 for Windows (SPSS Inc., Chicago, Illinois, USA) was used for the present calculations. Normal distribution of variables was calculated by the Kolmogorov–Smirnov test. Continuous data were presented as the mean ± standard deviation, and were compared by Student's *t*-test or Mann–Whitney *U*-test according to distribution. Categorical data were presented as proportions, and were compared with the χ^2-test and Fisher's exact test. A *P*-value <0.05 for two-tailed tests was considered significant. Kaplan–Meier analysis was used to evaluate the outcomes from the follow up.

RESULTS

Participant characteristics

A total of 173 participants aged 51–89 years were enrolled in the study. Based on the orthostatic BP screening criteria, participants were divided into an OH group and a non-OH group. There were 61 participants (35.26%) in the OH group and 112 (64.74%) in the non-OH group (Figure 1). The mean age of the study population was 70.04 ± 11.37 years, and males accounted for 56.65% of the patients. The mean age of patients in the OH group was 72.11 ± 11.80 years, and those in the
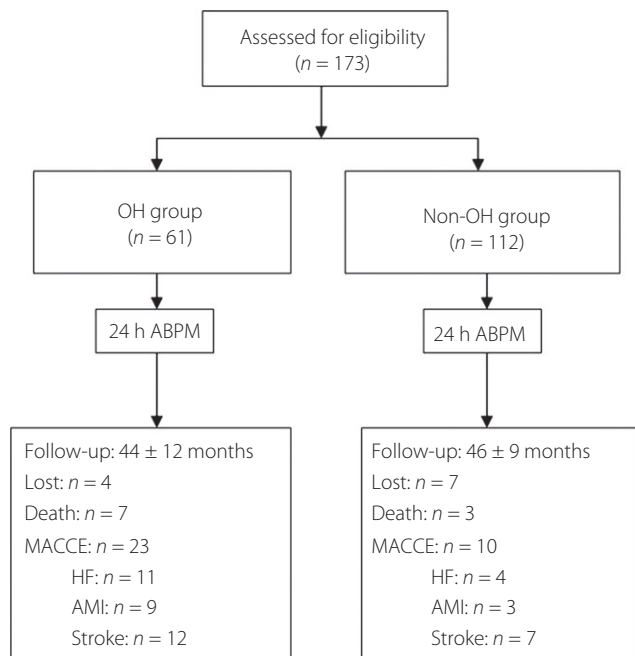
Figure 1 | Patient flow diagram. ABPM, ambulatory blood pressure monitoring; AMI, acute myocardial infarction; HF, heart failure; MACCE, major adverse cardiac and cerebrovascular events; OH, orthostatic hypotension.

non-OH group were 68.91 ± 11.03 years. In addition, the mean glycosylated hemoglobin (HbA1c) in the OH group was significantly higher than for those in the non-OH group (7.58 ± 1.25% vs 7.02 ± 1.18%, $P < 0.01$). There were no statistically significant differences in the BMI, medical history, antihypertensive drug use and other biochemical data between the two groups (Table 1).

Ambulatory BP monitoring

There was no statistically significant difference of the 24-h ambulatory BP monitoring, as well as the average SBP and DBP in the whole-day and in the daytime among the two groups (Table 1). The average night-time SBP and DBP in the OH group were both significantly higher than those in the non-OH group (139.44 ± 12.35 mmHg vs 131.32 ± 14.30 mmHg, $P < 0.01$; 79.11 ± 10.51 mmHg vs 71.88 ± 10.53 mmHg, $P < 0.01$). The circadian rhythm for BP in the OH group was predominantly the riser type (67.21%), whereas in the non-OH group it was the non-dipper type (55.36%; Figure 2).

There was a significant difference of HbA1c between the OH group and the non-OH group at baseline. Multinomial logistic regression was carried out. There was no relationship between the HbA1c and BP circadian rhythm by multivariate analysis. After adjustment for the confounding factors by multinomial logistic regression, including age, sex, HbA1c and BMI, OH was as an independent marker of riser type circadian rhythm

(adjusted odds ratio 4.532, 95% confidence interval 2.579–7.966).

Outcomes from the follow up

The participants were followed up for an average period of 45 ± 10 months. The OH group and non-OH group were followed for 44 ± 12 months and 46 ± 9 months, respectively. There were four and seven participants lost to follow up in the two groups, respectively (Figure 1). In the OH group, six participants with riser type (6/41, 14.63%) and one participant with non-dipper type (1/11, 9.09%) died, and in the non-OH group, one participant with extreme type (1/3, 33.33%) and two participants with riser type (2/24, 8.33%) died, respectively. In total, in the OH group and non-OH group, seven and three patients died. There was a significant difference of mortality between the OH group and the non-OH group (11.48 vs 2.68%, $P = 0.014$). The incidence of heart failure and myocardial infarction in the OH group and non-OH group were 11 (18.03%) vs four (3.57%), and nine (14.75%) vs three (2.68%), respectively. Strokes were reported in 12 and 7 cases, respectively. Some participants developed heart failure after myocardial infarction, and others had strokes combined with myocardial infarction or heart failure. Therefore, the MACCE were 23 and 10 participants in the OH group and non-OH group, respectively. There were distinct differences of MACCE among participants between the two groups (37.70 vs 8.93%, $P < 0.01$). The Kaplan–Meier survival curves of these two groups are shown in the Figure 3.

DISCUSSION

In the present prospective cohort study, 173 patients with type 2 diabetes were recruited; the prevalence of OH was 35.26%. Mortality and the incidence of MACCE in the OH group were significantly higher than that in the non-OH group after an average follow-up period of 45 months. OH, a manifestation of autonomic nervous dysfunction, results from inadequate hemodynamic accommodation through the cardiovascular regulatory mechanisms when body position changes from supine to standing erect. Gravitational changes lead to decreased venous return, reduced cardiac output and resultant decreased BP. It was reported in the literature that the prevalence rate of OH ranged from 5 to 30%[1,4]. Compared with normal individuals, the rate of OH is higher in diabetes patients[1,14]. Clinicians have gradually attached importance to OH in a setting of diabetic neuropathy. A recent multicenter study by Chou et al.[15] enrolled 13,486 patients with an average age of 54.8 ± 19.0 years; over a follow-up period of 4.5 ± 2.9 years, they found that OH was an independent risk factor for stroke and all-cause mortality[15]. Another recent meta-analysis[16] of 121,913 patients followed for an average of 6 years concluded that OH led to increased all-cause mortality, coronary heart disease, heart failure and stroke. However, heterogeneity in that meta-analysis was high (85–95%, except for coronary disease whose heterogeneity was 35%). The source of the heterogeneity was

Table 1 | Baseline characteristics of patients

	With OH group (*n* = 61)	Without OH group (*n* = 112)	*P*-value
Age (years)	72.11 ± 11.80	68.91 ± 11.03	0.077
Male *n* (%)	32 (52.46%)	66 (58.93%)	0.427
BMI (kg/m^2)	24.35 ± 3.64	25.32 ± 3.39	0.082
Medical history			
Ischemic heart, *n* (%)	13 (21.31%)	21 (18.75%)	0.693
Hypertension, *n* (%)	40 (65.57%)	59 (52.68%)	0.110
Cerebrovascular disease, *n* (%)	15 (24.59%)	24 (21.43%)	0.704
Current smoker, *n* (%)	19 (31.15%)	37 (33.04%)	0.866
Biochemical data			
Total cholesterol (mmol/L)	4.39 ± 1.01	4.47 ± 0.99	0.625
LDL cholesterol (mmol/L)	2.28 ± 0.74	2.38 ± 0.74	0.417
HDL cholesterol (mmol/L)	1.17 ± 0.36	1.18 ± 0.32	0.810
Triglycerides (mmol/L)	1.48 ± 1.26	1.45 ± 1.33	0.889
HbA1c (%)	7.58 ± 1.25	7.02 ± 1.18	0.004
Creatinine (μmol/L)	98.73 ± 19.29	93.69 ± 15.00	0.059
Medications			
Oral hypoglycemic drugs, *n* (%)	57 (93.44%)	98 (87.50%)	0.300
Insulin therapy, *n* (%)	20 (32.79%)	42 (37.50%)	0.619
Antiplatelets, *n* (%)	17 (27.87%)	28 (25.00%)	0.719
Beta-blockers, *n* (%)	18 (29.50%)	31 (27.69)	0.860
CCB, *n* (%)	17 (27.87%)	28 (25.00%)	0.719
Diuretics, *n* (%)	7 (11.48%)	11 (9.82%)	0.796
ACEI/ARB, *n* (%)	28 (45.90%)	47 (41.96%)	0.633
Statins, *n* (%)	32 (52.46%)	61 (54.46%)	0.874
Standing test			
Supine SBP (mmHg)	135.13 ± 14.26	132.64 ± 16.24	0.317
Supine DBP (mmHg)	74.51 ± 10.87	72.96 ± 10.75	0.367
Supine HR (b.p.m.)	69.61 ± 8.37	69.04 ± 8.98	0.688
Standing SBP (mmHg)	120.74 ± 14.11	130.90 ± 18.72	<0.001
Standing DBP (mmHg)	68.03 ± 10.46	72.78 ± 10.67	0.005
Standing HR (b.p.m.)	72.70 ± 8.55	73.47 ± 8.41	0.569
24-h Ambulatory blood pressure			
24-h SBP (mmHg)	135.75 ± 12.75	133.63 ± 13.06	0.305
24-h DBP (mmHg)	75.89 ± 10.64	73.65 ± 10.52	0.186
Daytime SBP (mmHg)	132.90 ± 12.85	136.38 ± 14.40	0.117
Daytime DBP (mmHg)	73.70 ± 10.82	76.13 ± 12.82	0.211
Night-time SBP (mmHg)	139.44 ± 12.35	131.32 ± 14.30	<0.001
Night-time DBP (mmHg)	79.11 ± 10.51	71.88 ± 10.53	<0.001
24-h HR (b.p.m.)	69.97 ± 8.63	69.17 ± 9.19	0.578

Data are shown as mean ± standard deviation for continuous variables, and percentages (%) for categorical variables. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; BMI, body mass index; CCB, calcium channel blockers; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein; SBP, systolic blood pressure.

unclear. Therefore, further research is required to verify the relation between OH and prognosis[16]. Finally, a retrospective study of 10 years of follow-up data in type 1 and type 2 diabetes patients reported prevalence rates of OH of 31.7 and 32.3%, respectively, and that the presence of OH was associated with an increased risk of vascular diseases, myocardial infarction, stroke and death[12].

In the present study, 24-h ambulatory BP monitoring was used to evaluate the BP circadian rhythm in participants with diabetes and OH, and it was found that the riser type was

common in this population. Multiple logistic regression analysis was used to explore the possible association between OH and BP circadian rhythm. After adjustment for baseline characteristics, OH was significantly associated with the riser type circadian rhythm (adjusted odds ratio 4.532, 95% CI: 2.579–7.966). The 24-h ambulatory BP monitoring is a useful non-invasive technique for evaluating patients with labile hypertension or episodes of hypotension, as it can reflect the patients' BP fluctuations and circadian rhythms, and thus offers advantages over traditional office BP measurement[17,18]. Elevated night-time BP
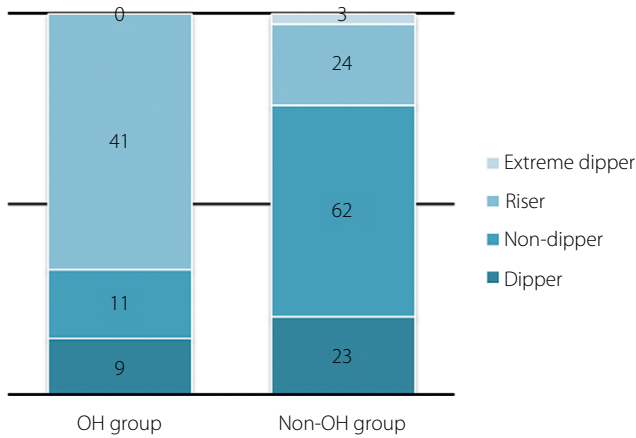
Figure 2 | Compare blood pressure circadian rhythms for diabetes patients with or without orthostatic hypotension (OH).
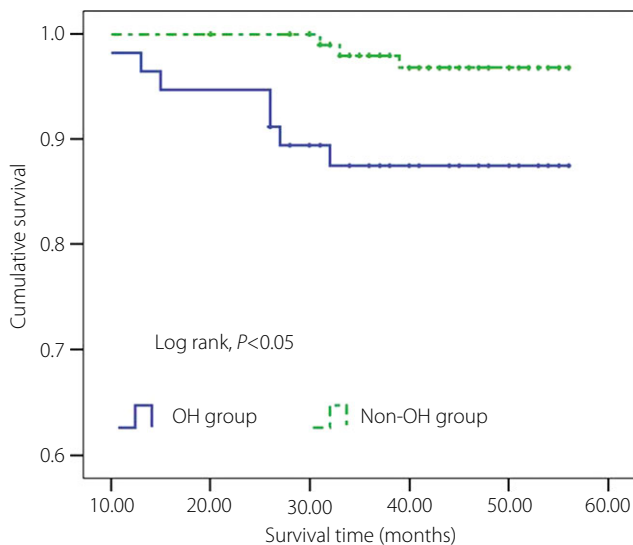

Figure 3 | Kaplan–Meier survival curves of the orthostatic hypotension (OH) group and non-OH group.

and non-dipping profiles have been evaluated in several studies, and it has been shown that elevated night-time BP, or inverted dippers, is associated with vascular damage, cardiovascular risk and mortality[19,20].

OH patients can be symptomatic, with dizziness, weakness, nausea, back pain and/or syncope. However, a majority of patients with this diagnosis are asymptomatic in normal conditions as a result of adequate compensatory mechanisms[21,22]. Therefore, it is important to diagnose OH in diabetes patients early, and attempt to reduce adverse events. Obtaining orthostatic BP measurements in the supine and standing position is very feasible, and can adequately screen for OH. Thus, this technique has clear clinical application in diabetes patients, along with 24-h ambulatory BP monitoring for studies of riser patterns of nocturnal BP changes.

The role of drug treatment for patients with OH is limited at present, given the side-effects of the available agents[23]. Therefore, patient education is the primary therapeutic approach for OH. It can help the patient understand the physiological mechanisms of the symptoms that follow body position changes, the inducing and aggravating factors for OH, and possible strategies for avoidance of the symptoms and syncope[24]. BP regulation is a complicated physiological process that involves cardiovascular, nervous, renal and endocrine inputs. Receptor activation by autoantibodies to β-adrenergic and muscarinic receptors is reported to lead to vasodilation and OH[25]. The mechanism of OH leading to clinical syndromes might involve impaired hemodynamic homeostasis, in which neuroendocrine compensatory mechanisms are intermittently activated. These mechanisms can trigger other effects, such as platelet and/or coagulation cascade activation, which in turn induce further cardiovascular or cerebrovascular events. Excessive activation of the endothelial system in patients with syncope has been implicated in some forms of OH[26]. Finally, it has been reported that OH patients are characterized by high BP variability and high night-time BP, with increased afterload; this might lead to target organ injury, such as left ventricular hypertrophy and reduced renal function, and give rise to heart failure and myocardial ischemia[27].

The strength of the current study was the use of a prospective cohort with type 2 diabetes mellitus that has been followed longitudinally for 45 ± 10 months. The relationship between the BP circadian rhythms and outcomes in diabetes with OH was analyzed. We found that in patients who had type 2 diabetes diagnosed with OH, the BP circadian rhythm usually showed riser patterns, and they had increased rates of mortality and major adverse cardiac and cerebrovascular events. A limitation of the present study was that it was carried out in a single center with a small patient sample, and might limit the generalizability of the results to the whole population.

In summary, patients with combined diabetes and OH frequently have high night-time SBPs and DBPs (characterized as the riser type of circadian rhythm), and associated risk of increased mortality and MACCE.

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DISCLOSURE

The authors declare no conflict of interest.

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