https://doi.org/10.46389/rjd-2022-1119
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2022; volume 29, issue 3, pages 273-279

Original Article

Prevalence of white-coat and masked hypertension in patients with type 2 diabetes

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Received: 20 January 2022 / Accepted: 13 March 2022

Abstract

Concurrent measurement of office blood pressure (BP) and 24-hour monitoring of BP is an effective method for diagnosing white and masked hypertension, two pathological conditions associated with increased cardiovascular risk. We aimed to investigate the prevalence of white-coat and masked hypertension in a cohort of patients with type 2 diabetes. We randomly recruited 260 patients with type 2 diabetes and hypertension in our cross-sectional study. Anthropometric, clinical, and laboratory data were collected and all patients were submitted to 24-hour ambulatory BP monitoring. Participants were 61.1±7.9 years old, 102 (39.2%) men, and had a median duration of diabetes of 10.0 (5.0; 15.0) years. We found that the prevalence of white-coat hypertension and masked hypertension was present in 13% and 43.5%, respectively. In our patients with type 2 diabetes, we observed a lower prevalence of white-coat hypertension and a higher prevalence of masked hypertension compared to previous data reported in the general population. Our observation draws attention to the importance of office BP and 24-hour ambulatory BP measurements in patients with type 2 diabetes.

Keywords: white coat hypertension, masked hypertension, ambulatory blood pressure monitoring, type 2 diabetes mellitus, hypertension.

Introduction

Arterial hypertension is a frequent comorbidity of type 2 diabetes and they are both well-known risk factors for atherosclerotic cardiovascular disease and vascular-related death [1]. Substantial evidence supports the benefits of effective blood pressure (BP) control in preventing cardiovascular outcomes in patients with type 2 diabetes and hypertension [2, 3]. BP assessment over the course of a day better predicted health outcomes such as all-cause and cardiovascular mortality than BP measured in the office or at home [4, 5]. The recent guideline for the management of hypertension published by the European Society of Cardiology (ESC)/European Society of Hypertension (ESH) recommends concomitant measurement of BP in the office and during 24-hour ambulatory blood pressure measurement (ABPM) to identify patients with white-coat hypertension (WCH) and masked uncontrolled hypertension (MH) [6, 7].

WCH refers to an increased office BP despite a normal out-of-office BP investigated using home and 24-hour ABPM. Conversely, MH refers to hypertensive patients presenting with increased mean BP when measured by home monitoring and/or 24-hour ABPM and normal BP in the office [6–8]. The prevalence of WCH was reported to be 15 to 25% in persons attending the clinic. Women at older ages and smokers were more likely to be diagnosed with WCH [9–11]. MH was found in 10% to 40% of patients with normal office BP, and

it was more prevalent among young men, currently smokers with obesity, diabetes and chronic kidney disease. [7, 12–14]. The terms WCH and MH were originally defined for people not being treated for hypertension. Nowadays, they are also used to describe discrepancies between office and out-of-office BP in patients treated for hypertension [8]. Both WCH and MH in normotensive and treated hypertensive individuals were associated with all-cause and cardiovascular mortality, while MH was a stronger risk predictor [10]. There is a 3 to 4 times higher risk for progression from normotension to sustained hypertension in the presence of WCH and MH [15]. Patients with the hypertensive phenotype of WCH were found to have an increased cardiovascular risk compared to their normotensive peers [16, 17]. Similarly, patients with MH were found to have a higher risk for cardiovascular events compared to their peers with normotension or WCH [18].

The prevalence of WCH in patients with diabetes evaluated using 24-hour ABPM were less likely to have WCH than those without diabetes [14, 19]. Conversely, MH was reported to be higher in patients with diabetes [14] compared to their normoglycemic peers, and it was found to be associated with an increased risk of cardiovascular events, especially when nighttime BP was elevated [20]. Overall, it appears that the caveat for the evaluation of hypertension may fail to detect masked BP elevations in patients with type 2 diabetes rather than failing to notice WCH [21]. In addition, the assessment of WCH and MH in patients with diabetes became more complicated because the cut-off value for target BP measured in the office varies according to different guidelines [6, 9]. Given all these findings regarding WCH and MH in patients with hypertension and diabetes, we aimed to investigate their prevalence in a cohort of patients with type 2 diabetes and treated hypertension.

Material and methods

Study design and patients

In our cross-sectional study, we randomly recruited a number of 260 adult patients with type 2 diabetes mellitus and hypertension presenting for a routine visit at the Centre of Diabetes, Nutrition and Metabolic Diseases, County Emergency Hospital Cluj-Napoca, Romania, from July 2013 to July 2018. The study protocol was approved by the local Ethics Committee of the Iuliu Haţieganu University of Medicine and Pharmacy Cluj-Napoca, Romania, in accordance with institutional and national guidelines and the Helsinki Declaration. All patients included were aware of the investigational nature of the study and were able to sign an informed consent before any study procedure.

Type 2 diabetes and its chronic macrovascular and microvascular complications (atherosclerotic cardiovascular disease, peripheral neuropathy, retinopathy, nephropathy) were diagnosed according to American Diabetes Association criteria [22]. Hypertension was diagnosed according to the 2013 ESH/ESC guideline for the management of hypertension [9]. Patients were not included in the study if they were not receiving treatment for hypertension or if they were previously diagnosed with secondary hypertension, unstable cardiovascular conditions, renal or hepatic failure, were breastfeeding, or were pregnant.

Anthropometric and clinical data collection

Patients' data were collected through interviews and access to their medical records: name, age, gender, duration of hypertension and diabetes, smoking, comorbidities and chronic complications of diabetes and treatment of hypertension. Height, body weight, and abdominal circumference were measured and body mass index was calculated. Office BP was measured in both upper arms with the patient resting in a sitting position for at least 10 minutes using an automatic device (Colin Press-Mate BP-8800C Sphygmomanometer Monitor, Japan) and the highest BP value was recorded. Fasting blood samples were collected from all patients. HbA1c, blood glucose, and creatinine were assessed using commercially available methods in the accredited laboratory of Clinical County Emergency Hospital Cluj-Napoca, Romania. Glomerular filtration rate was estimated using the formula: https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr.

24-hour ambulatory blood pressure measurement

The arm with the higher BP was used for 24-hour ABPM. All patients were submitted to 24-hour ABPM using verified automatic oscillometric devices, HolCARD CR-07 (Aspel, Poland) and BTL-08 ABPM Recorder (BTL, United Kingdom). Office BP measurement was considered the reference for the diagnosis of WCH and MH. BP readings were obtained every 30 minutes during the day (7.00–22.00) and every 60 minutes (22.00–7.00) overnight. Patients were instructed to continue their everyday activities and to keep their arms relaxed and still during the BP measurement. All patients had data

 https://doi.org/10.46389/rjd-2022-1119

on at least 70% of the all-possible BP measurements. We calculated mean systolic and diastolic BP for each period: daytime, nighttime, and 24 hours [23].

The cut-off points for high office BP and 24-hour ABPM were defined according to the 2018 ESC/ESH Guidelines for managing hypertension. In the office, hypertension was defined by a conventional BP of ≥140/90 mmHg, and hypertension during 24-hour ABPM was defined as BP during 24 hours ≥130/80 mmHg, BP during daytime ≥135/85 mmHg, and BP during nighttime ≥120/70 mmHg (all equivalent to office BP≥140/90 mmHg) [6]. WCH was defined as elevated office BP despite controlled BP during 24-hour ABPM. MH was defined as normal office BP despite uncontrolled BP during 24-hour ABPM [6, 8].

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp). Kolmogorov–Smirnov test was used to test the normal distribution of all continuous variables. Data were expressed as mean±standard deviation or median and 25th and 75th percentiles, or numbers and percentages. A value of $p<0.05$ was considered statistically significant. Normally distributed variables were analyzed using the t-test, and non-normally distributed variables were analyzed using the Wilcoxon test. The value of $p<0.05$ is considered statistically significant.

Results

The characteristic of patients from the whole study group, patients without WCH and MH, patients with WCH, and patients with MH are presented in Table 1. Patients with WCH were less likely to be smokers than patients without WCH or MH ($p<0.001$). Patients with MH were more likely to be males ($p=0.048$), non-smokers ($p=0.007$), older ($p=0.018$), with a longer duration of diabetes ($p=0.043$), a lower estimated glomerular filtration rate ($p=0.022$) and to present with diabetic polyneuropathy ($p=0.035$) compared to patients without WCH or MH. Patients with WCH presented with a lower estimated glomerular filtration rate, but the difference did not reach statistical significance.

Table 1: Clinical and laboratory characteristics of participants.

Parameters	Study group (n=260)	The group without WCH or MH (n=159)	WCH Group (n=6)	MH Group (n=93)
Men, n (%)	102 (39.2%)	59 (37.1%)	4 (66.7%)	39 (41.9%) #
Age, years	61.1±7.9	60.2±7.7	63.2±6.0	62.7±8.0 #
Smokers, n (%)	35 (13.5%)	23 (14.5%)	0 (0.0%) #	12 (12.9%) #*
Waist circumference, cm	109.1±12.1	109.1±12.1	109.1±12.1	109.1±12.1
Body mass index, kg/m^2	32.2±5.3	32.2±5.3	32.2±5.3	32.2±5.3
Diabetes duration, years	10.0 (5.0; 15.0)	9.0 (4.0; 15.0)	10.0 (8.0; 15.0)	11.0 (6.0; 14.5) #
Hypertension duration, years	10.0 (6.0; 14.0)	10.0 (6.0; 14.0)	10.5 (7.0; 15.0)	10.0 (6.0; 14.5)
Fasting glycemia, mg/dL	170.0±49.0	173.3±50.4	171.5±47.7	164.1±50.0
HbA1c, %	9.4±2.2	9.3±2.2	9.4±1.5	9.5±2.1
Estimated glomerular filtration rate, mL/min/1.73 m^2	73.0±21.4	75.9±20.6	60.0±20.0	69.5±20.1 #
Diabetic retinopathy, n (%)	103 (39.6%)	57 (35.8%)	2 (33.3%)	44 (47.3%)
Diabetic polyneuropathy, n (%)	164 (63.1%)	94 (59.1%)	2 (33.3%)	67 (72.0%) #
Diabetic nephropathy, n (%)	118 (45.4%)	70 (44.0%)	3 (50.0%)	45 (48.4%)
Atherosclerotic cardiovascular disease, n (%)	116 (44.6%)	65 (40.9%)	4 (66.7%)	47 (50.5%)

Note: N/n – number; % – percentage; BP – blood pressure; WCH – white-coat hypertension; MH – masked hypertension. # – $p<0.05$ for WCH group and MH compared to the group without WCH and MH; * – $p<0.05$ for the WCH group compared to the MH group.

The antihypertensive medication administered by patients from the whole study group, patients with WCH, patients with MH, and patients without WCH and MH, is presented in Table 2. All patients with WCH were using angiotensin-converting enzyme inhibitors and none of them were using angiotensin II receptor blockers, adrenergic α-antagonists, potassium-sparing diuretics, or loop diuretics. Patients with MH were less likely to administer thiazide diuretics than patients in the group without WCH or MH (p=0.002).

BP in the office and mean BP evaluated during the daytime, nighttime and 24-hour periods using 24-hour ABPM in the study population, controlled hypertension and uncontrolled hypertension, WCH, and MH groups are presented in Table 3.

Office BP≥140/90 mmHg was found in 127 (48.8%) of the whole sample. According to 24-hour BP control, we found a number of 46 (17.7%) patients with controlled hypertension and 214 (82.3%) patients with uncontrolled hypertension. A total of 6 patients out of those with controlled hypertension were identified as having WCH, and a total of 93 patients out of those with uncontrolled hypertension were identified as having MH. The prevalence of WCH was 13.0% and the prevalence of MH was 43.5%.

Discussion

In the present study, we investigated the prevalence of white-coat and masked hypertension in a cohort of patients with type 2 diabetes and hypertension treated at a tertiary center. WCH was found in 13.0% of patients. In the current literature, it has been reported that the prevalence of WCH was 17.3% in the general population [10]. In the Spanish ABPM Registry analyses, the largest ABPM patient database worldwide, including both untreated and treated hypertensive patients, WCH was reported in 27.2% of treated hypertensive patients [11]. In patients with diabetes and treated hypertension, the prevalence of WCH was reported to be 17.1% [9], while in patients who did not use antihypertensive drugs had a higher prevalence of 40% to 55% [24]. We found a lower prevalence of WCH in our patients with type 2 diabetes. One possible explanation for our finding might be related to the presence of certain diabetes complications such as autonomic neuropathy [25] and, thus, a lower reactivity to clinic stress. Another explanation might be related to study samples and cut-off points for BP. We found a low number of patients presenting with WCH. Automatic BP measurement in the office without medical staff in the same examination room as the patient might reduce the WCH phenomenon and does not influence the MH phenomenon [7]. Unattended office BP measurement might have resulted in an even lower prevalence of WCH in our study population, but it was not feasible given certain settings in our clinical practice.

We found that most individuals had BP inadequately controlled during 24-hour ABPM when evaluated using 24-hour ABPM. The prevalence of MH in our study was 43.5%, and it was higher than in other studies re-

Table 2: Antihypertensive medication.

Parameters	Study group (n=260)	The group without WCH or MH (n=159)	WCH Group (n=6)	MH Group (n=93)
Angiotensin-converting enzyme inhibitors, n (%)	150 (57.7%)	81 (50.9%)	6 (100.0%) #	52 (55.9%) *
Angiotensin II receptor blockers, n (%)	80 (30.8%)	49 (30.8%)	0 (0.0%) #	30 (32.3%) *
Beta-blockers, n (%)	162 (62.3%)	94 (59.1%)	3 (50.0%)	65 (69.9%)
Calcium channel blockers, n (%)	92 (35.4%)	58 (36.5%)	4 (66.7%)	29 (31.2%)
Adrenergic α-antagonists, n (%)	19 (7.3%)	15 (9.4%)	0 (0.0%) #	4 (4.3%)
Thiazide diuretics, n (%)	125 (48.1%)	89 (56.0%)	3 (50.0%)	33 (35.5%) #
Potassium-sparing diuretics, n (%)	32 (12.3%)	23 (14.5%)	0 (0.0%) #	9 (9.7%) *
Loop diuretics, n (%)	44 (16.9%)	27 (17.0%)	0 (0.0%) #	17 (18.3%) *

Note: N/n – number; % – percentage; BP – blood pressure; WCH – white-coat hypertension; MH – masked hypertension. # – p<0.001 for the WCH group and MH group compared to the group without WCH and MH; * – p<0.001 for the WCH group compared to the MH group.

https://doi.org/10.46389/rjd-2022-1119

Table 3: Blood pressure measured in the office and during 24-hour ambulatory blood pressure monitoring.

Blood pressure (mmHg)	Study group (n=260)	Controlled hypertension (n=46)	Uncontrolled hypertension (n=214)	WCH (n=6)	MH (n=93)
Office BP					
Systolic	136.9±17.7	122.9±13.0	139.9±17.1	133.8±15.2	126.3±7.4
Diastolic	80.4±12.0	76.7±10.2	81.2±12.2	88.8±8.7	74.6±9.1
24-hour ABPM					
Systolic mean					
24-hour	131.4±15.5	114.2±7.0	135.1±14.3	116.3±8.0	127.8±11.6
Daytime	133.2±15.2	116.4±7.6	136.8±14.0	119.3±8.9	129.2±10.4
Nighttime	126.9±17.1	107.2±7.0	131.2±15.6	106.9±6.7	124.9±14.1
Diastolic mean					
24-hour	80.1±11.7	68.8±4.8	82.5±11.3	71.0±7.8	79.1±9.6
Daytime	81.8±11.9	70.6±5.4	84.2±11.6	72.9±9.2	80.6±9.9
Nighttime	75.7±13.0	63.0±4.4	78.5±12.5	65.0±4.1	76.0±10.4

Note: BP – blood pressure; WCH – white-coat hypertension; MH – masked hypertension. Values are expressed as mean±standard deviation.

ported in the literature involving patients with diabetes and treated hypertension. This suggests that more than one-third of patients with type 2 diabetes who are considered to have adequate BP control in the office do not have their BP controlled when evaluated by 24-hour ABPM. Banegas *et al.* reported that the proportion of MH among well-controlled treated hypertensive patients in the clinic was 31.1% and that the prevalence was significantly higher in those with diabetes than in their counterparts [13]. In previous studies, including patients with diabetes, the prevalence of MH was 30% [26], 47% [27, 28] in untreated hypertensive patients, and 18.8% in treated hypertensive patients [14]. Our findings are in accordance with findings from the literature.

Cut-off points were chosen for controlled office BP, and 24-hour ABPM might have influenced the prevalence of the hypertensive phenotypes WCH and MH. The 2013 ESH/ESC guidelines for managing hypertension recommend office BP to be lower than 140/90 in the general population and lower than 140/85 mmHg in patients with diabetes [9]. On the other hand, the new 2018 ESC/ESH Guidelines for the management of hypertension recommend an office BP to be lower than 140/90 in the general population, lower than 130/80 mmHg in adult patients with diabetes younger than 65 years, and lower than 140/80 mmHg in patients with diabetes older than 65 years [6]. Although the office BP targets were changed for certain populations, the office BP and 24-hour ABPM targets were not changed accordingly, resulting in a discrepancy between previous and current recommendations [6]. In agreement with 2013 ESH/ESC guidelines, a position paper by O'Brien *et al.* proposes the use of office BP readings higher than 140/90 mmHg and a mean 24-hour BP higher than 130/80 mmHg for the diagnosis of WCH, and office readings lower than 140/90 mmHg and a mean 24-hour BP lower than 130/80 mmHg for the diagnosis of MH [8]. In our study, we used the office and out-of-office BP cut-offs recommended by the 2013 and 2018 ESH/ESC guidelines for managing hypertension for the general population [6, 9] and the 2021 European Society of Hypertension practice guidelines [7]. Other studies reporting the prevalence of WCH [10] and MH [13, 29] in the general population used the reference 140/90 mmHg for office BP, according to 2013 ESH/ESC guidelines for the management of arterial hypertension [9].

White-coat hypertension defines elevated office BP in untreated normal BP patients, while white-coat uncontrolled hypertension describes the difference between an elevated office BP and a normal home or ambulatory BP in treated hypertensive patients [8]. This observation could explain the different prevalence reported in the literature for these clinical conditions, related to the definition and the criteria selection for

the population studied (treated or untreated, population-based, or referred hypertensive patients) and type of out-of-clinic BP measurement. Banegas *et al.* reported white-coat hypertension and white-coat uncontrolled hypertension separately [10], while Sierra *et al.* reported the prevalence of white-coat hypertension in treated and untreated patients depending on all daytime, nighttime, and 24-hour BP, only daytime, or only 24-hour BP [11].

Similarly, the difference between masked hypertension and masked controlled hypertension should be pointed out. Masked hypertension term defines untreated patients in whom the BP is normal in the office but is elevated when measured by ABPM [6]. On the other side, the definition of masked uncontrolled hypertension refers to treated hypertensive patients in whom BP levels are suboptimal controlled according to ABPM but who are considered to be controlled according to clinic BP targets [8]. MH has gone unrecognized for a long time because few studies reported using ABPM to determine the prevalence of suboptimal BP control in seemingly well-treated hypertensive patients [28].

The 2013 and 2018 ESC/ESH Guidelines for the management of arterial hypertension, the 2020 International Society of Hypertension (ISH) Hypertension Guidelines and the 2017 Report of the American College of Cardiology/American Heart Association on hypertension extensively address the issue of WCH and MH in untreated and treated hypertensive patients and offer data regarding prevalence, diagnosis, and prognosis [6, 9, 30, 31]. In the Hypertension Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension, masked and white coat hypertension are defined based on office BP measurements and home BP readings, while white coat effect is recommended to be monitored using home or ambulatory BP monitoring [32]. The 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults Joint National Committee (JNC) 8 does not address the issue of white-coat or masked hypertension [33].

The results of our study might have potential implications for managing patients with type 2 diabetes and hypertension. It draws attention to the need for both office BP and 24-hour ambulatory BP measurements in this category of patients to detect WCH and MH, two clinical conditions with confirmed implications for further cardiovascular and all-mortality risk. On the other hand, it identifies patients with MH as a subgroup at higher risk that should represent a priority for access to ambulatory BP monitoring and further adjustment of antihypertensive medication.

Our study has several limitations. We diagnosed WCH and MH based on office BP and 24-hour ABPM. No information on home BP monitoring was available that might have provided complementary and somewhat different data. The second limitation of our study is the arbitrary definition of daytime and nighttime periods. Although this method has been previously reported in other studies and international consensus [34, 35], recent guidelines recommend using patient diaries to document activity and rest cycles [9]. Another limitation of our study was the low number of persons identified as having WCH, resulting in difficulty characterizing the group with the hypertensive phenotype of WCH.

Conclusions

We found a lower prevalence of white-coat hypertension and a higher prevalence of masked hypertension in patients with type 2 diabetes and treated hypertension compared to data reported in the general population. Our observation could be explained by the presence of type 2 diabetes and might indicate a higher cardiovascular risk in these patients. In addition, our study draws attention to the importance of office blood pressure and 24-hour ambulatory blood pressure measurements in this category of patients.

Conflict of interest

The authors declare no conflict of interest.

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