Masked uncontrolled hypertension: Prevalence and predictors

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ABSTRACT

Background: There are limited data on ‘masked uncontrolled hypertension’ (MUCH) in patients with treated and apparently well-controlled BP is unknown.

Objectives: To define the prevalence and predictors of MUCH among hypertensive patients with controlled office blood pressure.

Methods: One hundred ninety-nine hypertensive patients presented to the specialized hypertension clinics at two University Hospitals. All patients had controlled office blood pressure (less than 140/90 mmHg). Patients were assessed regarding history, clinical examination, and laboratory data. All patients underwent ambulatory blood pressure monitoring (ABPM) for 24 h, within a week after the index office visit. MUCH was diagnosed if average 24-h ABPM was elevated (systolic BP ≥ 130 mmHg and/or diastolic BP > 80 mmHg) despite controlled clinic BP.

Results: Sixty-six patients (33.2%) had MUCH according to 24-h ABPM criteria (mean age 53.5 ± 9.3 years, 60.6% men). MUCH was mostly caused by the poor control of nocturnal BP; with the percentage of patients in whom MUCH was solely attributable to an elevated nocturnal BP almost double that due to daytime BP elevation (57.3% vs. 27.1%, P < 0.001). The most common predictors of MUCH were smoking, DM and positive family history of DM.

Conclusion: The prevalence of masked suboptimal BP control is high. Office BP monitoring alone is thus inadequate to ascertain optimal BP control because many patients have an elevated nocturnal BP. ABPM is needed to confirm proper BP control, especially in patients with high cardiovascular risk profile. Smoking, DM and positive family history of DM were the most common predictors of MUCH.

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1. Introduction

Masked hypertension (MH) is a term used to define people who have a normal seated clinic blood pressure (BP) but an elevated out-of-office BP, as determined by ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM). Masked hypertension is the opposite of the more commonly recognized ‘white coat hypertension’. Patients with MH are now known to be at particularly high risk of developing cardiovascular disease (CVD) because they often remain undetected and untreated.

Most studies on the prevalence of MH have primarily focused on ‘treatment naive’ patients, prior to the diagnosis of hypertension, and many of them based the measurements on HBPM or daytime ABPM, or were of small size.1 This daytime definition of MH didn’t include people whose sole abnormality is an elevation in nocturnal BP, which some studies suggest is the strongest predictor of CVD risk compared with daytime or 24-h mean pressures.2 Furthermore, few studies have established the prevalence of the equivalent of MH, i.e. ‘masked uncontrolled hypertension; MUCH’, in patients with treated hypertension. MUCH is used to describe treated patients in whom BP levels are sub-optimally controlled according to ABPM, but who are considered controlled according to clinic BP targets by current treatment guidelines recommendations (<140/90 mmHg). Despite the recognized potential for clinic BP alone to both over- and under diagnose hypertension, to date,
few guidelines, as NICE 2011 guidelines have recommended the routine use of ABPM to monitor the quality of BP control because there are very little data on the quality of BP control in routine clinical practice.3

The aim of this study is to determine the prevalence and predictors of MUCH in hypertensive patients with controlled office BP.

2. Methods

This is a prospective, non-randomized, observational, cross sectional study that enrolled 199 HTN patients who presented to the specialized HTN clinics at two university hospitals. Patients were recruited from February 2016 to June 2017. Inclusion included hypertensive patients on regular antihypertensive treatment who had controlled office blood pressure readings (less than 140/90 mmHg and ≤140/85 for diabetics, for at least two visits, one month apart).4 Excluded from the study were those with secondary hypertension, acute myocardial infarction, significant valvular heart disease, decompensated heart failure (New York Heart Association class III and IV), and pregnant ladies.

Patients gave informed consent about being included in this study. They underwent full clinical evaluation including cardiovascular risk factors assessment e.g. history of diabetes mellitus, smoking and their duration, current medications, family history of CV risk factors and current antihypertensive drugs (class and dosage).

Examination included: assessment of the body mass index (BMI) (Obesity is defined as BMI > 30 Kg/m²), waist circumference, supine heart rate, peripheral pulses as well as searching for signs of target organ damage.

Blood pressure measurement was done using a digital fully automated device (Omron-6 automated device).5 Patients were allowed to rest for 3–5 min before measurement. Three BP readings were taken, 1–3 min apart, the first one was omitted and the last two readings were averaged. Patients were allowed to stand unsupported for 2 min and then standing BP readings were recorded.

Laboratory workup included (Hemoglobin level, serum Creatinine, potassium, total cholesterol, low density lipoprotein, high density lipoprotein, and triglycerides, fasting blood sugar and uric acid). Fundus examination was asked for to detect significant hypertensive retinopathy (> grade II hypertensive retinopathy). Urine analysis was performed in all studied patients, those who had proteinuria underwent albumin creatinine (A/C) ratio. Patients with abnormal A/C ratio (defined as having albuminuria above 30 mg/dl) are considered to have proteinuria as a marker of target organ damage.6

Standard 12 lead ECG was done in all patients. Abnormalities as arrhythmias, premature beats, ischemic heart disease, conduction defects and left ventricular hypertrophy (LVH) were documented. Criteria for LVH diagnosis with ECG were followed.7

Target organ damage (TOD) including: LVH, carotid bruit, hypertensive retinopathy ≥ grade II, peripheral arterial disease, and clinical CVD (coronary heart disease, congestive heart failure) were diagnosed, using the appropriate investigation, and were documented. Chronic renal disease was diagnosed when serum creatinine was >1.3 mg/dl and/or when proteinuria was present.

All patients underwent 24-hour ABPM. ABPM was conducted on the patient’s non-dominant arm using Holter system Model DMS 300-4A2 with device set to measure the BP every half an hour in daytime and every hour during the night, according to the patient’s sleep and awake times. The patients were asked to continue performing their normal routines but remain still during the measurements. Blood pressure measurement performed for all patients on all days of the working week. Average day, night, and 24-hour blood pressure and pulse rate of patients were collected.

Dipping (i.e. nocturnal blood pressure fall) has been categorized into four groups: (6) (a) normal dipping; where the ratio between mean night systolic and mean day systolic is (0.8–0.9), (b) no dipping; where the ratio is (0.9–1), (c) reverse dipping; the ratio is more than 1 and (d) extreme dipping; the ratio is less than 0.8.

Valid ABPM recordings had to fulfill a series of pre-established criteria, including successful recording of ≥80% of systolic BP (SBP) and diastolic BP (DBP) during both the daytime and nocturnal periods, and at least one BP measurement per hour.

The primary aim is to detect the prevalence of MUCH which is defined as: (6) normal office BP and, (a) mean awake ABPM readings ≥135/85 and/or (b) mean night ABPM readings ≥120/70 and/or (c) mean average 24H ABPM readings ≥130/80.

2.1. Statistical analysis

Quantitative variables were expressed as mean and standard deviation (SD), while qualitative variables were presented as numbers and percentages.

We divided the study patients into two groups; group 1 with normal office and normal mean 24 h ABPM, (controlled HTN) and group 2 with normal office and elevated mean 24 h ABPM, (masked HTN, (MUCH)).

We compared the two groups regarding demographics, risk factors, target organ damage and other parameters by means of Chi-square/Fisher exact test for categorical data, and student t-test for continuous data. Linear Regression analysis was used to detect predictors of MUCH. All statistical tests were 2 sided, and we judged a P-value of <0.05 to be significant. All analyses were carried out using SPSS 20.

3. Results

Demographic and clinical characteristics of patients are demonstrated in Table 1. Most patients were middle aged. About one third had diabetes mellitus (DM) and one third were current heavy cigarette smokers.

The data obtained from the Ambulatory BP analysis shows that about two-thirds of patients had non-dipping or reversed dipping patterns in nocturnal BP readings.

About one third of patients (n = 66, 33.2%) were diagnosed to have MUCH, according to 24-hours ABPM readings. Taking only day time ABPM, 54 (27.1%) patients had MUCH, while when using only nighttime BP, 114 (57.2%) patients had MUCH. Nighttime ABPM seems to cause greater impact on the high prevalence of MUCH found in 24-hours average ABPM analysis. Diagnosis of MUCH (in 24-hours average BP) is mainly due to combined elevation of both systolic and diastolic BP (48%) rather than elevated only systolic (30.3%) or only diastolic (21.2%) blood pressures.

Characteristically, patients with MUCH had more prevalence of cardiovascular risk factors; higher prevalence of DM, dyslipidemia, heart failure, smoking and higher prevalence of positive family history of HTN and DM. They also had inadequate response to standing as compared to the controlled HTN group.

Both groups showed comparable results regarding the prescribed antihypertensive medication. Fig. 1. The most frequently prescribed anti-hypertensive drug, in both groups, was beta blocker and the least prescribed was diuretic.

Laboratory workup of patients with MUCH is shown in Table 2. No characteristic laboratory difference was found between the 2 groups.

Linear regression analysis showed that the most significant predictors of MUCH were smoking, DM, and a positive family history of DM, Table 3.
Table 1
Clinical profile of patients with MUCH versus patients with controlled BP.

| Variable                | Patients with MUCH (n = 66), No (%) | Patients with controlled HTN (n = 133), No (%) | P value |
|-------------------------|-------------------------------------|-----------------------------------------------|---------|
| Gender, Male            | 40 (60.6)                           | 54 (40.6)                                     | 0.008   |
| Age, years (Mean ± SD)  | 53.5 ± 9.3                          | 53.8 ± 10.5                                   | 0.8     |
| Non-employed            | 22 (33.3)                           | 63 (47.4)                                     | 0.06    |
| Illiterate              | 13 (19.7)                           | 37 (27.8)                                     | 0.21    |
| Associated comorbidities|                                     |                                               |         |
| Diabetes mellitus       | 44 (66.7)                           | 64 (48.1)                                     | 0.013   |
| Dyslipidemia            | 11 (16.7)                           | 9 (6.8)                                       | 0.029   |
| Known CKD               | 8 (12.1)                            | 6 (4.5)                                       | 0.048   |
| CAD                     | 6 (9.1)                             | 14 (10.5)                                     | 0.8     |
| History of stroke       | 4 (6.1)                             | 5 (3.8)                                       | 0.5     |
| Heart Failure           | 4 (6.1)                             | 1 (0.8)                                       | 0.042   |
| Smokers                 | 30 (45.5)                           | 26 (19.5)                                     | <0.001  |
| Family history of HTN   | 46 (68.7)                           | 77 (57.9)                                     | <0.001  |
| Family history of DM    | 51 (77.3)                           | 49 (36.8)                                     | <0.001  |
| Abnormal ECG            | 27 (40.9)                           | 35 (26.3)                                     | 0.04    |
| Abnormal fundus examination (n = 176) | 12 (19.7) | 13 (11.3)                                     | 0.13    |
| TOD                     | 37 (56.1)                           | 38 (28.6)                                     | <0.001  |

BMI; Body mass index, BP; Blood pressure, CAD; Coronary artery disease, CKD; Chronic kidney disease, DBP; Diastolic blood pressure, DM; Diabetes mellitus, ECG; Electrocardiogram, HTN; Hypertension, MUCH; Masked uncontrolled hypertension, SBP; Systolic blood pressure, TOD; Target organ damage.

Significant p values are marked in bold.

Fig. 1. Percentage of prescribed antihypertensive drugs in both study groups. MUCH; Masked uncontrolled hypertension; HTN; Hypertension, BB; Beta blockers, CCB; Calcium channel blockers, ACEI; Angiotensin enzyme inhibitor, ARBs; Angiotensin receptor blockers.

Table 2
Laboratory characteristics of MUCH patients versus controlled HTN patients.

| Variable               | Patients with MUCH (n = 66), Mean ± SD | Patients with controlled HTN (n = 133), Mean ± SD | P value |
|------------------------|----------------------------------------|--------------------------------------------------|---------|
| Serum creatinine       | 1.1 ± 0.5                              | 1.1 ± 1.0                                        | 0.8     |
| Fasting blood sugar    | 107.2 ± 30.8                           | 100.6 ± 26.7                                     | 0.1     |
| Total Cholesterol      | 172.0 ± 25.6                           | 174.9 ± 34.2                                     | 0.6     |
| LDL-Cholesterol        | 115.9 ± 21.9                           | 114.2 ± 26.8                                     | 0.7     |
| HDL-Cholesterol        | 46.9 ± 6.3                             | 46.3 ± 8.8                                       | 0.7     |
| Triglycerides          | 161.1 ± 32.0                           | 154.8 ± 37.0                                     | 0.3     |
| Uric acid              | 5.6 ± 1.3                              | 6.4 ± 5.8                                        | 0.5     |
| Serum                  | 4.2 ± 0.4                              | 4.2 ± 0.3                                        | 0.9     |
| Potassium              | 13.1 ± 1.1                             | 13.3 ± 1.2                                       | 0.2     |

HDL; High density lipoprotein, HTN; Hypertension, LDL; Low density lipoprotein, MUCH; Masked uncontrolled hypertension.
Nighttime BP is known to be a strong predictor factor for total, cardiovascular, stroke and cardiac mortality.\textsuperscript{21} Elevated night time BP showed a great impact on the prevalence of MUCH in our study as 57.3\% of the patients proved to have MUCH using only nighttime BP vs. 27.1\% when only daytime BP was used. About 80\% of patients reported marked discomfort with the device especially at night and they were awakened from sleep by cuff inflations. The resulting disturbed sleep rhythm may have altered sympathetic activity leading to nocturnal surge of BP.

Results from the Spanish registry\textsuperscript{17} showed lower prevalence of nocturnal HTN (24.3\% vs 57.3\% in our study).

One of the findings of this study is that patients with MUCH showed higher standing SBP compared to those with controlled BP. An inverse relationship between BP response to standing and the difference between clinic BP and daytime BP was documented before. Compared to patients with normal reaction to standing, patients with increased reaction showed higher levels of systolic and diastolic ABPM.\textsuperscript{22} Such data indicate that increased reactivity to standing is predictive of higher ABPM and explain the reason why patient with MUCH had higher standing SBP in our study.

This study showed that patients with MUCH had high prevalence of cardiovascular risk factors and TOD which is concordant to what reported by Pickering et al,\textsuperscript{23} the Spanish registry\textsuperscript{17} and Japan home study\textsuperscript{20} which signifies the importance of early detection and treatment of patients with MH since such patients are at increased risk of cardiovascular mortality and stroke.\textsuperscript{24} Whether the high-risk profile is a consequent or merely an association to MUCH is not yet known.

Using multivariate analysis, smoking, DM and family history of DM were found to be the strongest predictor of MH in our study. Bromfield et al\textsuperscript{25} also reported diabetes to be associated with a higher prevalence of masked daytime and isolated nocturnal uncontrolled hypertension among African Americans taking anti-hypertensive medication in the Jackson Heart Study. The Spanish registry\textsuperscript{17} showed that after multivariable adjustment, the odds ratio for masked 24-hour uncontrolled hypertension associated with diabetes taking antihypertensive medications was 1.25 (95\% CI = 1.14–1.37).

5. Limitations

This study has several limitations that we have to address. It was performed on a small sample size of hypertensive patients and a study on a larger number of patients from different geographic regions across the country is needed to verify our findings. Also, our study doesn't reflect the general population as patients were recruited from specialized HTN clinics and multicenter population-based study may be required. The diagnosis of MUCH was based on a single ABPM recording and would have been better to repeat the ABPM to test the reproducibility of MUCH diagnosis.

6. Conclusion

More than one third of patients showed MUCH despite apparently well controlled office BP readings. Elevated nocturnal BP was acting as a major determinant of the presence of MUCH, a finding which cannot be detected by regular clinic measurements. Patients with MUCH showed a higher constellation of traditional cardiovascular risk factors and TOD, which imposes tight BP control in order to reduce future cardiovascular events. Our recommendation is to suspect MUCH in apparently controlled HTN patients with high risk profile and to order ABPM for these patients for better evaluation and management of HTN.
Conflicts of interest

The authors declare that none of them had any conflict of interests.

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