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Research Article

Perception of uncontrolled blood pressure and non-adherence to anti-hypertensive agents in diabetic hypertensive patients

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Abstract

We assessed the association between adherence to antihypertensive drug treatment and patient's perception of uncontrolled blood pressure (BP) in diabetic hypertensive subjects. This was a cross-sectional study that evaluated adherence to antihypertensives (Morisky questionnaire), patients' perception of abnormal BP, office BP, and ambulatory BP monitoring in diabetic hypertensive subjects. We evaluated 323 patients, 65.2% women, aged 56.5 ± 7 years, glycosylated hemoglobin (HbA1c) 8.0% (range, 6.9%–9.6%), diabetes duration of 10 years (range, 5–17 years). Adherence to drug treatment was 51.4%. Patients who reported hypertension-related symptoms (60.4%) had a lower level of adherence ($P < .001$). Non-adherence occurred four times more frequently in patients who reported hypertension-related symptoms ($P < .001$, adjusted for use of three or more anti-hypertensives, age, and duration of diabetes). Non-adherents had higher office diastolic BP (83.6 ± 11.9 *vs.* 79.8 ± 9.9; $P = .003$), but no difference between groups was observed considering systolic, diastolic, and mean BP evaluated by ambulatory BP monitoring. Low rates of adherence to antihypertensive drug treatment were observed in outpatient hypertensive diabetic subjects. Perception of uncontrolled BP levels was strongly and independently associated with non-adherence. Non-adherence determined repercussion on office BP that may have clinical implications in cardiovascular risk. J Am Soc Hypertens 2013;7(6):477–483.

Keywords: Diabetes mellitus; hypertension; medication adherence.

Introduction

Hypertension and diabetes cause significant morbidity and mortality around the world. In Brazil, chronic non-communicable diseases are the main cause of death,[1] and the association of diabetes with hypertension determines 8.5-times greater risk for cardiovascular disease.[2] Clinical trials have shown that lowering blood pressure (BP) levels by drug treatment reduces the risk of fatal and nonfatal cardiovascular events in hypertensive subjects with[3] and without[4] diabetes. However, effective BP control is difficult to achieve: the proportion of patients with uncontrolled BP can be as high as 30% to 40%[5,6] even in developed countries.[7] Non-adherence to drug therapy is acknowledged as a major contributor to the high prevalence of uncontrolled BP levels.[8] It is found in ∼50% of patients,[9] a number that was found to be up to 80% in high-risk Brazilian hypertensive subjects.[10]

The issue of non-adherence was explored from biomedical and behavioral viewpoints,[11] but few studies have been conducted from the perspective of patients. There are reports showing that the perception of illness influences non-adherence to treatments,[12] but in asymptomatic patients

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this influence did not occur.[13] In cross-sectional studies of convenience samples of hypertensive patients, illness perception and perceived severity of hypertension negatively influenced adherence to antihypertensives.[14] A qualitative study reported similar information in diabetic patients.[15] Although patients with hypertension are usually asymptomatic, many of them have the feeling that they can perceive uncontrolled BP levels. Patients' perceptions of adverse events associated with antihypertensive treatment may also contribute to non-adherence.[16] As patients with hypertension not using anti-hypertensive drugs may have a higher quality of life than those using these drugs,[17] this perception could lead to lower rates of adherence to treatment, ineffective BP control, and high rates of cardiovascular events.[18]

The aim of this study was to assess the association of adherence to antihypertensive drug treatment with patients' perception of uncontrolled BP in a sample of diabetic hypertensive subjects attending an outpatient clinic. In order to perform this assessment, patients were asked about their own perceptions concerning possible hypertension-related symptoms; their adherence was evaluated by the Morisky[19] questionnaire, and their BP was evaluated in the office and by 24-hour ambulatory blood pressure monitoring (ABPM).

Methods

This cross-sectional study is part of a broadest study - PRADHA (***P**erfil e **R**isco **A**nalisados no **D**iabetes e na **H**ipertensão **A**rterial*) that evaluated clinical variables in patients with diabetes and hypertension. This study was conducted in the Outpatient Clinic of the Hospital de Clínicas de Porto Alegre (Porto Alegre, RS, Brazil), which is a tertiary university hospital. The study was approved by the Ethics Committee of the Institution, and all patients signed a written informed consent before beginning the data collection.

The study population was selected from a consecutive sample of 2342 patients screened and recruited for participation from April 2010 to December 2011. Patients were included if they had hypertension (defined as current use of at least one anti-hypertensive or self-report of hypertension), type 2 diabetes (defined as current use of at least one anti-diabetic agent or self-report of diabetes), and were aged less than 65 years. All patients were aware of their hypertensive and diabetic status. Exclusion criteria were: body mass index (BMI) > 35 kg/m^2, previously diagnosed chronic illness, arrhythmias (atrial fibrillation) that could interfere with BP measurement, and patients with ABPM records with less than 6 and 18 measures during the night and the day periods, respectively.[18] According to these criteria, 323 patients were included (Figure 1).

Patients who met the inclusion criteria and agreed to participate underwent a demographic and clinical baseline data collection, including the assessment of duration of diabetes and its known chronic complications, smoking, previous cardiovascular diseases, medication in use, BMI, and BP levels. BP was measured twice after 15 minutes of rest with an automatic sphygmomanometer (ONROM HEM-705 CP; OMRON, Matsuzaka, Mie, Japan) and cuff appropriate for arm circumference. For the final analysis, we used the average between the two BP measurements. High office BP levels were defined as BP $>$130/80 mm Hg.[8] In this first visit, subjects were unaware of the aim of the study, which was presented for them when they arrived.

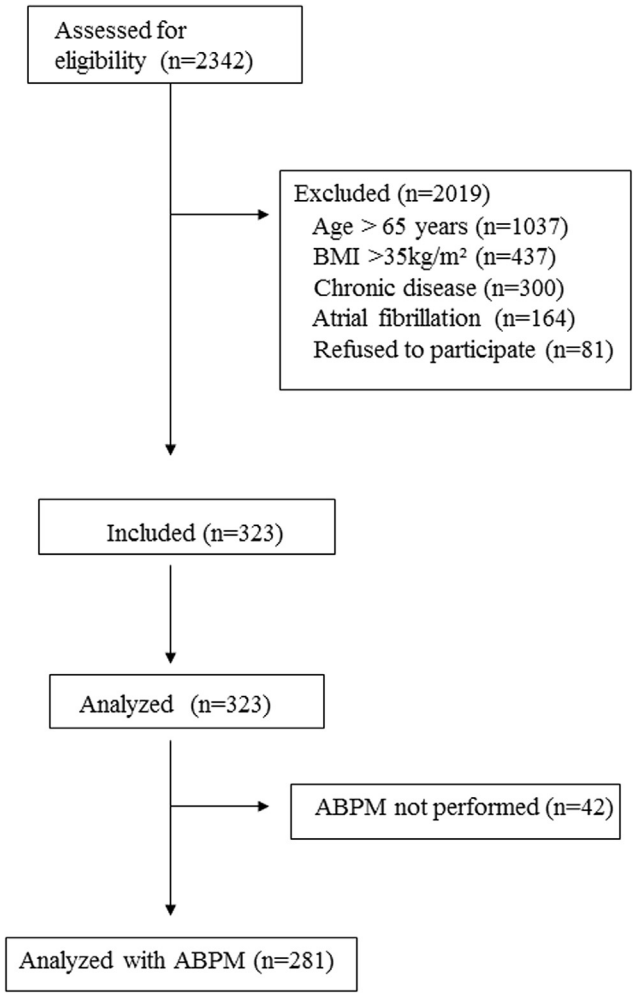

Figure 1. Flow chart of participants. ABPM, ambulatory blood pressure monitoring; BMI, body mass index.

Instrument used to evaluate adherence to pharmacological treatment was the Morisky questionnaire, in a validated Portuguese version.[19] It was applied by an investigator not blinded to BP measurement. Participants were considered to be adherent by the Morisky questionnaire when they answered "no" to four questions in the questionnaire; answering "no" to three or fewer questions classified them as non-adherent.[10]

To evaluate perception of uncontrolled BP, patients were asked: "Do you feel when your BP is altered?" For those

who answered "yes," they were asked which symptoms they usually experience. The most frequent answers were headache, neck pain, visual disturbance, epistaxis, and tinnitus, which were analyzed. Other symptoms were very infrequent, and thus were not considered.

Among the selected individuals, 86.9% (n = 281) were submitted to ABPM in a normal working day (Spacelabs 90,207; Spacelabs, Redmond, WA),[20] which was usually performed no more than 1 to 2 weeks after the initial evaluation. Readings were obtained at 15-minute intervals during the day and 20-minute intervals during the night, for 24 hours throughout the period studied. Based on the ABPM results, the mean 24-hour systolic (SBP) and diastolic (DBP) BPs were calculated for each patient. High 24-hour ABPM levels were defined as BP >130/80 mm Hg.[21]

Blood samples were obtained in the fasting state using commercial kits for laboratory analysis of the following parameters: Plasma glucose was measured by a glucose oxidase method, serum creatinine by Jaffé's reaction, and HbA1c by ion-exchange HPLC (Merck-Hitachi L-9100 HbA_{1c} analyzer; reference range 4.8%–6.0%; Merck, Darmstadt, Germany). Serum total cholesterol and triglycerides were measured by enzymatic-colorimetric methods (Merck Diagnostica, Darmstadt, Germany; Boehringer Mannheim, Buenos Aires, Argentina) and high density lipoprotein (HDL) cholesterol by a homogeneous direct method (auto-analyzer, ADVIA 1650, Siemens Healthcare Diagnostics, Eschborn, Germany). Low-density lipoprotein (LDL) cholesterol was calculated using Friedewald's formula. Glomerular filtration rate was calculated using the Modification of Diet in Renal Disease equation.

Statistical Analysis

The groups for comparison were defined as adherent and non-adherent by the Morisky questionnaire. Student *t*-test, Mann-Whitney *U* tests, and χ^2 test were used to compare the characteristics of the groups, as appropriate. Results are expressed as median and 95% confidence interval (CI) or mean ± standard deviation. Logistic regression models were used to evaluate the association between adherence and perception of abnormal BP. Duration of diabetes, age, and use of three or more anti-hypertensives were included in the model. *P* values <.05 (two-tailed) were considered to be statistically significant. Statistical Package for Social Science (SPSS, Chicago, IL), version 18.0, was used for the analyses.

Results

We studied 323 patients, aged 56.5 ± 7 years, most of them women. Table 1 describes baseline variables, disease characteristics, medication use, and clinical variables evaluated in all the study population. Moreover, differences among groups according to their adherence to anti-hypertensive treatment are described.

Adherence to antihypertensive drug treatment evaluated by the Morisky questionnaire was present in 166 (51.4%) of patients. There were more smokers or former smokers in the adherent group. There was no difference in the number of antihypertensive drugs used between the groups: in both groups, most patients used three or more antihypertensive medications (53.4% in adherents, 57.0% in non-adherents). Metabolic control, as evaluated by glycemia and HbA1c, was similar between adherent and non-adherent patients, but cholesterol levels were higher in non-adherents.

Table 2 shows the symptoms reported by patients and their BP levels according to adherence (Morisky questionnaire). All symptoms were more frequently reported by non-adherents. The most common symptoms were headache, neck pain, and visual disturbance. Dizziness and tinnitus were less frequent. There were no BP differences among individuals who reported having abnormal BP perception vs. those who did not. Reports on perception of uncontrolled BP were more frequent among non-adherent patients.

Non-adherent individuals had higher office DBP (83.6 ± 11.9 mm Hg vs. 79.8 ± 9.9 mm Hg; $P = .003$) as compared with adherents, but no difference was observed taking SBP into account. There were no differences in SBP, DBP, and mean BP evaluated by ABPM between adherents and non-adherents.

Figure 2 describes the variables associated with non-adherence. According to the model, non-adherence was not associated with duration of diabetes, age, and use of three or more anti-hypertensive, but was positively associated with the perception of abnormal BP. The perception of uncontrolled BP by patients was strongly and independently associated with non-adherence to medications (odds ratio, 4.4; 95% confidence interval, 2.42-8.13; $P < .001$).

Discussion

In the present study, we showed that just over half of outpatient hypertensive diabetic patients treated in a tertiary center adhere to antihypertensive drug treatment. As hypothesized previously, patients' perception of uncontrolled BP levels was strongly and independently associated with non-adherence. Non-adherence determined repercussion on office BP levels, but not on ABPM levels.

Importantly, as this was a cross-sectional study, reversal of causality should be taken into account as a reason of different interpretations of the findings obtained. The finding that perception of uncontrolled BP because of symptoms was associated with lower adherence may lead to the interpretation that perception is the cause of low adherence or that low adherence provokes more symptoms, because the patients are aware that they are not following medical recommendations. Both statements are valid, and the answer of which is correct cannot be obtained by a cross-sectional design. However, assuming these opposite interpretations as potentially right, another utility of looking at the patient's

Table 1
Clinical characteristics of all patients studied and comparing adherents and non-adherents (Morisky questionnaire)

Characteristic	All (N = 323)	Adherents (N = 166)	Non-adherents (N = 157)	*P*
Women	210 (65.2)	110 (66.3)	100 (64.1)	.772
Age, years	56.5 ± 7.0	57.5 ± 5.7	56.5 ± 7.1	.164
Caucasian	217 (68.9)	119 (73.0)	98 (64.5)	.242
Education				.642
Primary school	196 (60.6)	104 (62.6)	92 (58.6)	
High school	79 (24.4)	34 (20.5)	45 (28.6)	
Tertiary school	18 (5.6)	10 (6.0)	8 (5.0)	
Family history				
Diabetes mellitus	237 (79.0)	118 (74.7)	119 (83.8)	.073
Cardiovascular disease	90 (30.2)	57 (35.8)	33 (23.7)	.068
Diabetes duration (years)	10 (5–17)	11 (6–18)	10 (4–17)	.170
Smoking				.045
Never smoked	167 (55.1)	78 (48.4)	89 (62.7)	
Current smoker	35 (11.6)	21 (13.0)	14 (9.9)	
Former smoker	101 (33.3)	62 (38.5)	39 (27.5)	
Previous cardiovascular disease	97 (30)	54 (32.5)	43 (27.4)	.333
BMI (kg/m^2)				.060
<25	30 (9.6)	11 (6.8)	19 (12.8)	
25–30	120 (38.6)	71 (43.8)	49 (32.9)	
>30	161 (51.8)	80 (49.4)	81 (54.4)	
Medications in use				
Metformin	279 (88.3)	144 (88.3)	135 (88.2)	1.000
Sulfonylureas	108 (34.2)	57 (35.0)	51 (33.3)	.851
Insulin	159 (50.3)	73 (44.8)	86 (56.2)	.055
Diuretics	257 (81.6)	129 (79.1)	128 (84.2)	.310
ACEI	243 (77.6)	124 (77.0)	119 (78.3)	.893
ARA2	27 (8.6)	15 (9.3)	12 (7.9)	.818
Calcium channel blockers	105 (33.4)	56 (34.6)	49 (32.2)	.751
Beta-blockers	164 (52.2)	82 (50.6)	82 (53.9)	.633
Vasodilators	60 (15.9)	26 (16.0)	24 (15.8)	1.000
Antiplatelet	205 (65.3)	105 (64.8)	100 (65.8)	.950
Statins	207 (66.1)	111 (68.9)	96 (63.2)	.356
Number of antihypertensive drugs in use				.732
1	44 (14.1)	25 (15.3)	19 (12.6)	
2	97 (30.9)	51 (31.3)	46 (30.5)	
3 or more	173 (55.1)	87 (53.4)	86 (57.0)	
Plasma glucose (mg/dl)	151.5 ± 66.3	150.8 ± 68.1	153.9 ± 67.0	.750
HbA1c (%)	8.0 (6.9–9.6)	7.8 (6.9–9.1)	8.2 (7.0–10.0)	.255
Total cholesterol (mg/dl)	179.9 ± 45.2	173.5 ± 43.6	187.2 ± 46.3	.035
HDL cholesterol (mg/dl)	44.1 ± 17.5	43.2 ± 12.0	45.0 ± 21.6	.476
Triglycerides (mg/dl)	151.0 (104.0–231.0)	142.2 (102.0–206.0)	173.0 (114.0–239.5)	.105
GFR (ml/h)	88.5 ± 28.7	86.8 ± 29.4	89.7 ± 28.1	.847

ARA2, angiotensin receptor antagonist 2; ACEI, angiotensin-converting enzyme inhibitor; BMI, body mass index; GFR, glomerular filtration rate calculated by the Modification of Diet in Renal Disease equation.

Continuous variables are expressed as mean ± standard deviation or median (interquartile range).

Categorical variables are expressed as number (%).

perception of uncontrolled BP can be raised: perception of uncontrolled BP could be a sign of low adherence, as a consequence to be feeling ''guilty'' for not being good patients. It should be noticed that the patients themselves knew the secret, that they were not taking their pills correctly.

This is the first study to evaluate adherence rates in diabetic hypertensive subjects in a clinical setting. The adherence rates reported here were similar to those found in national[22] and international[23,24] surveys in hypertensive only patients. The adherence rate of 88% reported by Bloch et al[10] was much higher than all others reported. However, that study was performed in resistant hypertensive patients who were followed up at specialized outpatient clinics.

We chose to use the Morisky questionnaire to categorize subjects, since it is more widely used[19,20,25] and could be

Table 2
Symptoms reported by the patients studied and blood pressure levels comparing adherents and non-adherents

Characteristic	Adherents (N = 166)	Non-adherents (N = 157)	*P*
Perception of abnormal blood pressure	78 (47.0)	113 (72.0)	<.001
Headache	39 (23.4)	57 (36.3)	<.001
Neck pain	33 (18.8)	43 (27.3)	<.001
Visual disturbance	22 (13.2)	43 (27.3)	<.001
Dizziness	15 (9.0)	24 (15.2)	<.001
Tinnitus	10 (6.0)	23 (14.6)	<.001
SBP office (mm Hg)	141.6 ± 19.2	142.1 ± 17.5	.808
DBP office (mm Hg)	79.8 ± 9.9	83.6 ± 11.9	.003
ABPM (mm Hg)			
24-hour SBP	131.0 ± 12.4	131.5 ± 13.8	.767
24-hour DBP	77.1 ± 12.2	77.1 ± 8.7	.995
Daytime SBP	133.4 ± 17.3	134.4 ± 14.7	.712
Daytime DBP	79.8 ± 12.8	79.7 ± 9.9	.955
Nighttime SBP	123.1 ± 18.2	123.4 ± 16.6	.917
Nighttime DBP	69.1 ± 10.5	69.7 ± 9.8	.627

ABPM, ambulatory blood pressure monitoring (data available for 281 subjects); DBP, diastolic blood pressure; SBP, systolic blood pressure.

Variables are expressed as number (%), χ^2, or as mean ± standard deviation.

more practical in the daily care of hypertensive diabetic patients. In general, the performance of the Morisky questionnaire is considered very good, with a positive predictive value of 91.6%.[26] The methods available for measuring adherence can be broken down into direct and indirect methods of measurement; each has advantages and disadvantages, and no method is considered the gold standard.[27] In the case of hypertension, the measurement of the hallmark of the disease (BP) would be the best marker of adherence, but short-term background variability and additional longer-term variability in an individual's BP level are drawbacks to be deal with. These issues seems likely to influence the capacity to correctly discriminate between adherent and non-adherent patients, which will be worse in long-term than in the early treatment period.[28] In contrast, patient interview methods have been found to correlate well with adherence to BP-lowering therapy.[29]

In the present study, 59.1% of subjects reported the ability to discern their BP control. Literature reports that 28%[30] to 72%[31] of hypertensive patients have a perception of BP changes, but no study was performed specifically with diabetic hypertensive subjects, who are a particular population, considering clinical symptoms.[32] In our study, the most frequent symptoms were headache, neck pain, and visual disturbance, also similar to what is described in the literature.[22,31]

A good accuracy of the individual perception of BP levels is frequently reported by patients, although evidence shows the very opposite. In the present study, considering non-adherent subjects, 72% reported feeling when their BP was not well-controlled. In a study where patients were asked how they thought it was their BP before they had their BP evaluated, 86% of those who made predictions did not estimate their BP levels correctly.[33] Moreover, in a previous study by our group on hypertensive patients,[34] ~32% of them reported feeling a headache during the ABPM, but there were no BP differences between these patients as compared with those with no complaints.

Interestingly, although BP was similar between adherents and non-adherents when evaluated by ABPM, office DBP was higher in non-adherents. The fact that we found differences only in DBP can be explained by the average age of the patients (~56 years). In this age group, it is more frequently an increasing of DBP, as studies have shown that changing patterns of BP occur with increasing age.[35] The fact that we found differences only in office DBP can be explained simply by the fact that BP is more precisely measured by ABPM. We may also consider that all patients signed a written informed consent before beginning the data collection and answered the questionnaires on adherence and measured office BP before they had their ABPM evaluation. We hypothesize that they, intentionally or not, behaved better in the next few days and during the 24-hour exams, as an effect of the presence of the device.[36]

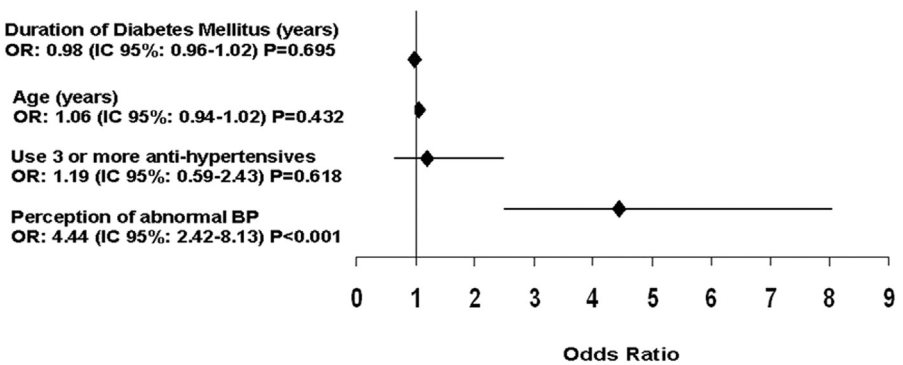

Figure 2. Association between non-adherence to pharmacological antihypertensive treatment with abnormal blood pressure perception adjusted for use of three or more antihypertensive medications, age, and duration of diabetes in multiple linear regression model. There was no interaction between the use of three or more antihypertensive medications, age, duration of diabetes, and adherence. 95% IC, 95% confidence interval; OR, odds ratio.

The results of a recent trial showing that a protocol of Home BP Monitoring (HBPM), without medication titration resulted in improving BP levels are in accordance with this hypothesis. The effect of HBPM over BP control probably resulted from behavioral modifications induced by the repeated awareness of BP levels by the patients. Patients could become more alert with respect to medication use and lifestyle choices, improving compliance with both pharmacological and non-pharmacological interventions to lower BP.[37]

The higher DBP (−3.8 mm Hg) observed in office measurements in non-adherents may have clinical implications since individuals with lower DBP have a lower risk of developing future cardiovascular events.[3,4] A recent systematic review showed that for each 2 mm Hg reduction in DBP, a 12% reduction of the likelihood of having a cardiac event is to be expected.[38] On the other hand, the fact that we did not find differences in ABPM raises doubt about the clinical implications of this finding.

The present study has potential limitations that should be noted. First, the office BP levels were taken by the same individual who applied the adhesion questionnaires. Because we used ABPMs, we do not think that this introduced a major bias into the measurements. Second, as adherence to any prescription is a complex issue, the modeling in logistic regression may not predict well the non-adherence. Finally, some limitation of external validity is expected, as more than 80% of outpatients were excluded. Moreover, increasing the sample size may allow more robust conclusions to be drawn from this study.

In conclusion, patients' perception of uncontrolled BP levels is strongly and independently associated with non-adherence. This belief is not harmless and should be demystified. Our results showed that non-adherence was associated with high office DBP levels and may, indirectly, be associated with future higher rates of cardiovascular events.

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