Impact of White-Coat Hypertension on Microvascular Complications in Type 2 Diabetes

CAROLINE K. KRAMER, MD
CRISTIANE B. LEITÃO, MD, PHD
LUÍS H. CANANI, MD, PHD
JORGE L. GROSS, MD, PHD

OBJECTIVE — The purpose of this study was to determine the impact of white-coat hypertension (WCH) on microvascular complications in type 2 diabetes.

RESEARCH DESIGN AND METHODS — A cross-sectional study was conducted in normotensive patients and patients with WCH selected from a cohort of 319 type 2 diabetic patients. Normotension was defined by office blood pressure <140/90 mmHg and daytime blood pressure <135/85 mmHg on ambulatory blood pressure monitoring (ABPM). WCH was defined as office blood pressure ≥140/90 mmHg and daytime blood pressure <135/85 mmHg on ABPM. Subjects were evaluated for diabetic nephropathy (24-h urinary albumin excretion rate) and diabetic retinopathy (classified according to the Global Diabetic Retinopathy Group).

RESULTS — Forty-six type 2 diabetic patients had WCH (14.4%; mean age 56.6 years; 45.3% men) and 117 had normotension (36.6%; mean age 55.8 years; 37.5% men). These groups did not differ in clinical and main laboratory characteristics. Systolic ABPM (24-h: 124.7 ± 6.7 vs. 121.0 ± 8.5 mmHg, $P = 0.01$ and daytime: 126.6 ± 7.2 vs. 123.2 ± 8.2 mmHg, $P = 0.01$) and blood pressure loads were higher in subjects with WCH than in the normotensive subjects. WCH was associated with an increased risk for macroalbuminuria (odds ratio 4.9 [95% CI 1.3–18.7], $P = 0.01$). On multivariate analysis models, WCH was associated with macroalbuminuria (2.0 [1.3–3.2], $P = 0.02$) and increased the risk for both nonproliferative and proliferative diabetic retinopathy (2.7 [1.2–6.6], $P = 0.02$ for any degree of diabetic retinopathy) after adjustments for confounding factors.

CONCLUSIONS — Type 2 diabetic patients with WCH have an increased risk for diabetic retinopathy and diabetic nephropathy. Therefore, WCH should not be considered a harmless condition, and treatment should be considered.

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Hypertension is a major risk factor for both the onset and progression of chronic diabetes complications, and its treatment can prevent deleterious micro- and macrovascular outcomes (1,2). Abnormalities in blood pressure homeostasis demonstrated on ambulatory blood pressure monitoring (ABPM) have a better correlation with target organ lesions than ordinary office blood pressure measurements (3,4).

Hypertensive patients with normal blood pressure values on ABPM, namely "white-coat hypertension" (WCH), have been historically considered to have a low risk profile for vascular complications. Consequently, subjects with WCH have been followed as normotensive individuals and, most of the time, do not receive treatment. However, emerging data from general population studies associate WCH with cardiac structural abnormalities (5) as well as increased risk for stroke and cardiovascular events (5).

In type 1 diabetic patients, WCH is associated with the subsequent development of sustained hypertension and microalbuminuria (6). However, the repercussions of WCH in type 2 diabetic patients have not been reported. Therefore, the aim of this study was to characterize type 2 diabetic patients with WCH and determine its effects on chronic diabetes complications.

RESEARCH DESIGN AND METHODS

— A cross-sectional study was performed with normotensive patients ($n = 117$) and patients with WCH ($n = 46$) selected from a cohort of 319 type 2 diabetic patients who had regularly attended the diabetes outpatient clinic at Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, since 1994. Normotension was defined by an office blood pressure <140/90 mmHg on at least two occasions during a 6-month period and daytime blood pressure means <135/85 mmHg on ABPM; WCH was defined by an office blood pressure ≥140/90 mmHg on at least two occasions during a 6-month period and daytime blood pressure means <135/85 mmHg on ABPM. None of the patients were taking antihypertensive medications at the time of evaluation, and those who were using any drug with an antihypertensive effect had the medication suspended 1 week before the evaluation. Patients with serum creatinine >1.5 mg/dl, other renal diseases, cardiac arrhythmia, autonomic symptoms (chronic diarrhea, syncope, or vasomotor symptoms), or orthostatic hypotension were excluded.

The study protocol was approved by the ethics committee of the hospital. Written informed consent was obtained from all patients.

Clinical evaluation

Patients underwent an interview and clinical examination to record demographic and anthropometric data, as described previously (7). Blood pressure evaluations were performed 1 week after withdrawal of all medications with an antihypertensive effect. The analyses were performed on the basis of the mean of two office blood pressure values (measured with a mercury sphygmomanometer us-

From the Endocrine Division, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.
Corresponding author: Caroline Kaercher Kramer, ckkramer@terra.com.br.
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ing the left arm and with the patient in a sitting position, after a 5-min rest, on the same day as the ABPM). ABPM was obtained by oscillometry (Spacelabs 90207 serial nos. 207/024751 and 207/038016 with calibration certification), with a 15-min interval in the daytime and 20-min interval in the nighttime period. ABPM was performed on an ordinary workday, and patients were advised to maintain their usual daily activities. Sleep time was recorded as the period between the time when the patient went to bed and the time when the patient woke up the next morning. The means of 24-h, daytime, and nighttime systolic and diastolic blood pressure were recorded, as well as systolic and diastolic blood pressure loads (percentage of 24-h and daytime blood pressure ≥140/90 mmHg and nighttime blood pressure ≥120/80 mmHg) and pulse pressure (systolic minus diastolic blood pressure). The difference between the office systolic blood pressure and daytime systolic blood pressure means was included in the analysis and described as the "white-coat effect."

Blood pressure was evaluated during exercise in a subset of patients (normotension $n = 38$ and WCH $n = 18$) by an exercise treadmill test (standard Bruce protocol using a computerized database) (8). Midway through each stage of the exercise protocol, at peak exercise and at 1, 2, and 4 minutes after cessation of exercise, data on symptoms, heart rate and rhythm, blood pressure, and estimated workload (based on standards tables) in METs (1 MET = 3.5 ml of oxygen uptake per kg body weight per min) were collected. The blood pressure increment was defined as the difference between the peak exercise blood pressure and resting blood pressure.

Laboratory methods

The urinary albumin excretion rate (UAER) was measured (values expressed in micrograms per minute) by immunoturbidimetry (MicroAlb Sera-Pak immunomicroalbuminuria [Bayer, Tarrytown, NY] on a Cobas Mira Plus analyzer [Roche]; mean intra-assay and interassay coefficients of variation of 4.5 and 7.6%, respectively) in at least two 24-h collections over the preceding 6 months (9). A1C was measured by a high-performance liquid chromatography system (reference range 4.7–6.0%) (Merck-Hitachi 9100; Merck, Darmstadt, Germany). Fasting plasma glucose was measured by the glucose-peroxidase colorimetric enzymatic method (Biodiagnostica). Serum creatinine was measured by the Jaffe method, serum total cholesterol and triglycerides were measured by enzymatic-colorimetric methods (Merck Diagnostica, Darmstadt, Germany; Boeringher Mannheim, Buenos Aires, Argentina), and HDL cholesterol was measured by the homogeneous direct method (ADVIA 1650 AutoAnalyzer). LDL cholesterol was calculated using the Friedenwald formula.

Table 1—*Clinical and laboratory characteristics according to blood pressure classification*

	Normotension	White-coat hypertension	*P* value
n	117	46	
Male subjects	53 (45.3)	17 (37.5)	0.38
Age (years)	56.6 ± 10.2	55.8 ± 9.6	0.65
Diabetes duration (years)	9.8 ± 7.9	10.9 ± 7.0	0.38
BMI (kg/m^2)	28.2 ± 5.0	28.8 ± 5.2	0.55
Waist circumference (cm)	97.7 ± 11.1	98.0 ± 12.5	0.62
Smoking habit	25 (21.6)	4 (8.9)	0.004
A1C (%)	6.9 ± 1.8	7.1 ± 1.8	0.61
Fasting plasma glucose (mg/dl)	159.4 ± 70.5	155.2 ± 57.0	0.73
Total cholesterol (mg/dl)	191.3 ± 39.4	194.0 ± 48.2	0.73
HDL (mg/dl)	48.2 ± 13.1	47.8 ± 10.1	0.87
LDL (mg/dl)	112.9 ± 33.1	114.0 ± 39.0	0.86
Triglycerides (mg/dl)*	122 (102)	121 (140)	0.86
Creatinine (mg/dl)	0.85 ± 0.2	0.82 ± 0.1	0.33
Estimated glomerular filtration rate (ml/min per 1.73 m^2)	90.8 ± 24.4	92.9 ± 23.9	0.63

Data are *n* (%) or means ± SD unless otherwise indicated. *Median interquartile range.

Outcomes

Diabetic retinopathy. Fundus eye examination was performed by an experienced ophthalmologist after mydriasis, and diabetic retinopathy was classified using the scale developed by the Global Diabetic Retinopathy Group (10). The diabetic retinopathy level was based on the most severe degree of retinopathy in the worst eye affected.

Diabetic nephropathy. UAER was measured in 24-h sterile urine samples. Patients were classified, according to UAER, into three groups: normoalbuminuric (UAER <20 μg/min), microalbuminuric (UAER 20–199 μg/min), and macroalbuminuric (UAER ≥200 μg/min). The glomerular filtration rate was estimated using the formula of the Modification of Diet in Renal Disease study: $186 \times [(\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742, \text{if female}) \times (1.210, \text{if African descendant})]$ (11).

Statistical analysis

All analyses were performed using the statistical package SPSS (version 14.0; SPSS, Chicago, IL). Data are expressed as means ± SD, except for UAER, triglycerides, blood pressure loads, and white-coat effect values, which are median (interquartile range). Quantitative variables without a normal distribution were log-transformed. Student's *t* test or χ^2 tests were used to compare clinical and laboratory data. Pearson's test was used to study correlations among clinical variables. Multiple linear regressions were performed with UAER as the dependent variable. Macroalbuminuria, microalbuminuria, and diabetic retinopathy were analyzed as dependent variables in separate models of logistic regression. $P < 0.05$ (two-tailed) on the univariate analysis were considered significant.

RESULTS — WCH was found in 46 (14.4%; mean age 56.6 years; 45.3% men) and normotension in 117 (36.6%; mean age 55.8 years; 37.5% men) type 2 diabetic patients of the overall cohort. These groups were not different regarding age, diabetes duration, anthropometric characteristics, renal function, glycemic control, or lipid profile (Table 1). Interestingly, there were more active smokers among the normotensive patients than among the patients with WCH.

The 24-h systolic blood pressure means on ABPM were higher in the WCH group than in the normotensive group

Table 2—*Blood pressure characteristics according to blood pressure classification*

	Normotension	White-coat hypertension	*P* value
n	117	46	
Office			
Systolic blood pressure (mmHg)	123.5 ± 10.8	149.7 ± 11.7	NA
Diastolic blood pressure (mmHg)	75.9 ± 7.3	88.5 ± 9.2	NA
Pulse pressure (mmHg)	47.5 ± 9.2	61.1 ± 13.8	<0.001
24 h			
Systolic blood pressure (mmHg)	121.0 ± 8.5	124.7 ± 6.7	0.01
Diastolic blood pressure (mmHg)	72.4 ± 6.0	72.7 ± 6.2	0.76
Pulse pressure (mmHg)	48.6 ± 7.6	52 ± 8.1	0.01
Systolic blood pressure load (%)	11.9 (24.2)	22.2 (21)	0.01
Diastolic blood pressure load (%)	3.3 (8.7)	6.3 (12.3)	0.03
Daytime			
Systolic blood pressure (mmHg)	123.2 ± 8.2	126.6 ± 7.2	0.01
Diastolic blood pressure (mmHg)	74.8 ± 6.4	74.8 ± 7.0	0.97
Pulse pressure (mmHg)	48.8 ± 8.8	51.7 ± 8.2	0.05
Systolic blood pressure load (%)	5.3 (13.2)	12.5 (19.3)	0.01
Diastolic blood pressure load (%)	2.3 (7.3)	4.5 (9.4)	0.04
Nighttime			
Systolic blood pressure (mmHg)	116.6 ± 11.8	119.8 ± 9.5	0.07
Diastolic blood pressure (mmHg)	66.8 ± 7.6	67.9 ± 7.3	0.39
Pulse pressure (mm Hg)	49.7 ± 8.6	51.9 ± 9.5	0.17
Systolic blood pressure load (%)	27.6 (64)	46.2 (34.4)	0.02
Diastolic blood pressure load (%)	2 (13.5)	6.7 (17.3)	0.06

Data are means ± SD or median (interquartile range).

(124.7 ± 6.7 vs. 121.0 ± 8.5 mmHg, P = 0.01). Daytime systolic blood pressure (126.6 ± 7.2 vs. 123.2 ± 8.2 mmHg, P = 0.01), pulse pressure (24 h 52 ± 8.1 vs. 48.6 ± 7.6 mmHg, P = 0.01 and daytime 51.7 ± 8.2 vs. 48.8 ± 8.8 mmHg, P = 0.05), and all blood pressure loads (24 h, daytime, and nighttime) followed the same pattern (Table 2).

WCH and microvascular complications

UAER was higher in patients with WCH than in normotensive patients (median 15.5 [interquartile range 45.3] vs. 7.4 [15.2] μg/min, P = 0.01). Moreover, the proportions of micro- and macroalbuminuric patients were higher in the WCH group (normoalbuminuria 57.1%, microalbuminuria 28.6%, and macroalbuminuria 14.3%) than in the normotensive group (normoalbuminuria 74.3%, microalbuminuria 21.9%, and macroalbuminuria 3.8%, P for trend = 0.03). WCH conferred an increased risk for macroalbuminuria (odds ratio [OR] 4.9 [95% CI 1.3–18.7], P = 0.01), but not for microalbuminuria (Fig. 1). This association was sustained after adjustments for diabetes duration and A1C in the multivariate regression model (2.0 [1.3–3.2], P = 0.02).

Similarly, a higher prevalence of diabetic retinopathy was found in patients with WCH than in normotensive patients (57.9 vs. 34.4%, P = 0.01). The presence of WCH increased the risk for both nonproliferative and proliferative diabetic retinopathy (Fig. 1). Moreover, WCH increased by 2.7-fold (95% CI 1.2–6.6) the chance for any degree of diabetic retinopathy after adjustment for diabetes duration and A1C (P = 0.02). Including current smoking habit in the multivariate regression models (for both UAER and diabetic retinopathy as outcomes) did not materially change the results.

The white-coat effect and microvascular complications

To evaluate whether the magnitude of WCH was associated with UAER, the difference between the office systolic blood pressure and daytime systolic blood pressure means (white-coat effect) was calculated. There was a correlation between this variable and UAER (r = 0.325, P = 0.04). In addition, in the linear regression model, the white-coat effect was associated with UAER independently of diabetes duration and A1C value (standardized β-coefficient 0.197, P = 0.03). In addition, patients with proliferative diabetic retinopathy (n = 26) presented with higher white-coat effect values (median 13 [interquartile range 26] mm Hg) than those without diabetic retinopathy or nonproliferative diabetic retinopathy (3 [21] mmHg, P = 0.04).

WCH and response to exercise

Thirty-eight normotensive patients and 18 patients with WCH performed exercise testing. The WCH group reached higher blood pressure maximum levels (systolic 183.7 ± 22.2 vs. 166.8 ± 16.1 mmHg, P = 0.002; diastolic 81.5 ± 7.3 vs. 76.4 ± 8.1 mmHg, P = 0.02) than the normotensive group. METs and peak exercise heart rate were similar between the

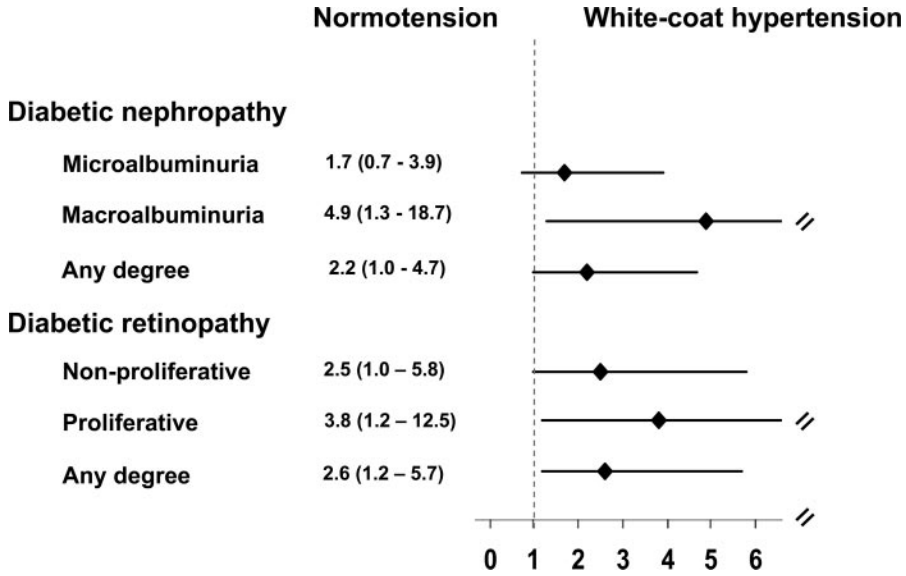

Figure 1—*WCH OR for type 2 diabetes chronic complications.*

Table 3—*Clinical and laboratory characteristics according to blood pressure classification*

	Normotension	White-coat hypertension	*P* value
n	38	18	
Resting systolic blood pressure (mmHg)	122.5 ± 15.3	130.6 ± 13.3	0.05
Resting diastolic blood pressure (mmHg)	77.8 ± 7.1	81.1 ± 6.7	0.11
Systolic blood pressure increase (mmHg)	44.3 ± 18.8	53.1 ± 18.5	0.10
Diastolic blood pressure increase (mmHg)	−1.3 ± 8.2	0.44 ± 7.7	0.43
Maximum systolic blood pressure (mmHg)	166.8 ± 16.1	183.7 ± 22.2	0.002
Maximum diastolic blood pressure (mmHg)	76.4 ± 8.1	81.5 ± 7.3	0.02
Total METs	8.1 ± 2.2	7.4 ± 1.5	0.24
Resting heart rate (beats/min)	84 ± 13.3	88.1 ± 10.4	0.26
Peak exercise heart rate (beats/min)	154.9 ± 17.7	160.5 ± 13.2	0.23

Data are means ± SD.

groups, demonstrating equivalent effort during the test (Table 3).

CONCLUSIONS — In this sample of type 2 diabetic subjects, the prevalence of WCH was 14%. The clinical and laboratory characteristics of these subjects did not differ from those of the normotensive group, but higher blood pressure levels were demonstrated during both the ABPM and exercise test. The presence of WCH increased the risk for diabetic retinopathy and macroalbuminuria by 2.7 and 2.0 times, respectively, after adjustment for confounders. In addition, the white-coat effect was positively correlated with UAER and also associated with proliferative diabetic retinopathy.

WCH is a common finding in both the hypertensive and general population, being described in 21–30 and 12%, respectively (5,12–14). The prevalence of WCH was believed to be increased in patients with diabetes, reaching up to 74% in hypertensive type 1 diabetic patients (15) and 51% in hypertensive type 2 diabetic patients (16). Subsequently, these findings were challenged in type 2 diabetic patients. Nielsen et al. (17) found a WCH prevalence of 23% in normoalbuminuric individuals, 8% in microalbuminuric patients, and 9% in macroalbuminuric patients. The overall prevalence of 14% in type 2 diabetic patients of this study is the same as that found in the general population and is close to the data of Nielsen et al. (17). Differences concerning the definition of WCH (systolic/diastolic 24-h blood pressure means or daytime systolic/diastolic blood pressure means) may have contributed to some of the disparities between the studies. Moreover, the prevalence of WCH changes according to age, sex, and ethnicity.

WCH has been historically treated as a benign phenomenon, as previous studies have demonstrated a lower risk for adverse events in this group than in those with sustained hypertension (18,19). This concept has been questioned lately, as WCH has come to be associated with greater left ventricular hypertrophy (5) and cardiovascular mortality (12,20,21). In the general population, some studies have shown similar clinical characteristics in individuals with WCH and normotensive individuals (22), whereas others have described a higher cardiovascular risk profile in subjects with WCH (23,24). Of interest is the fact that a current smoking habit was more frequent in the normotensive group. This could reflect a lifestyle change in subjects considered to be sicker, because they have increased levels in the office. However, in analysis of other vascular risk factors, such as dyslipidemia, obesity, glycemic control, and abdominal circumference, no difference was observed between groups. Even in the absence of a worse risk profile, WCH was associated with diabetic retinopathy and diabetic nephropathy. To the best of our knowledge, this is the first study to report an association between WCH and microvascular complications in type 2 diabetic patients.

The higher blood pressure peak demonstrated during the exercise test could be one example of how blood pressure responds to daily stressors in subjects with WCH. The WCH phenomenon may indeed reflect an abnormal and vigorous sympathetic response to environmental stimuli, which can be in the form of either mild physical activity or the presence of a health care professional. This acute rise in blood pressure levels could lead to glomerular and retinal damage. Patel et al. (25) demonstrated increased retinal flow after a rise in blood pressure in diabetic patients, suggesting that acute changes in blood pressure have a deleterious impact on retinal vessels. It is worth noting that all of the blood pressure loads in patients with WCH in our sample were higher than those in the normotensive individuals, suggesting acute and repeated rises in blood pressure levels, several times in the course of 24 h, during ordinary activities and probably also exercise.

The limitation of this report is mainly the cross-sectional design, which prevents the drawing of conclusions about the cause-and-effect relationship between WCH and the renal and retinal outcomes. However, this limitation does not detract from the main result of this study.

In summary, type 2 diabetic patients with WCH have an increased risk for microvascular complications. These findings indicate that WCH is not a benign situation in type 2 diabetic patients and most likely represents a phenotype intermediary between normotension and hypertension. Randomized controlled trials are needed to clarify the role of treatment of WCH in preventing type 2 diabetes-associated complications.

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