UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS:

ENDOCRINOLOGIA

HOMEOSTASE PRESSÓRICA NO DIABETES MELITO TIPO 2 E SÍNDROME METABÓLICA: COMPLICAÇÕES MICROANGIOPÁTICAS E CÁLCIO CORONARIANO

TESE DE DOUTORADO

CAROLINE KAERCHER KRAMER

Porto Alegre, novembro de 2009

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Tese de Doutorado apresentada ao Programa de Pós-Graduação em Ciências Médicas: Endocrinologia da Universidade Federal do Rio Grande do Sul (UFRGS) como requisito parcial para obtenção do título de Doutor em Endocrinologia.

Porto Alegre, novembro de 2009

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À minha mãe.

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LISTA DE ABREVIATURAS

ATP-III	*National Cholesterol Education Program - Adult treatment Panel III*
ABPM	*Ambulatory blood pressure monitoring*
A1c	*A1c test*
BMI	*Body mass index*
BP	*Blood pressure*
CAC	*Coronary artery calcium*
CHD	*Coronary heart disease*
CI	*Confidence interval*
CT	*Computed tomography*
DM	*Diabetes Mellitus*
DR	*Diabetic Retinopathy*
FPG	*Fasting plasma glucose*
HU	*Hounsfield units*
MESA	*Multi-Ethnic Study of Atherosclerosis*
OR	*Odds ratio*
UAER	*Urinary albumin excretion rate*
WCH	*White-coat hypertension*
WHO	*World health organization*

INTRODUÇÃO

A hipertensão arterial sistêmica é um fator de risco importante tanto para o desenvolvimento como para progressão das complicações crônicas do diabetes melito tipo 2 [1-2]. Nesse sentido, a avaliação da pressão arterial através da monitorização ambulatorial da pressão arterial (MAPA) tem demontrado melhor correlação com as lesões em órgao-alvo que as medidas de consultório [3-4].

A MAPA permite identificar alterações na homeostase pressórica nao identificadas somente com a medida de consultório, como a hipertensão mascarada, a hipertensão do avental branco e outras alterações na variablidade pressórica. Algumas dessas alterações como a hipertensão mascarada e o descenso noturno já foram relatadas em pacientes com diabete melito tipo 2 [3, 5]. Entretanto o efeito da hipertensão do avental branco e da variablidade pressórica em 24-h nas complicações crônicas do diabetes melito tipo 2 ainda não foi descrito e o seu papel necessita ser melhor elucidado.

A importância dos componentes individuais da Síndrome metabólica, em especial da pressão arterial, quanto ao desenvolvimento de desfechos clínicos tem sido bastante discutida na literatura. Estudo recente observou que os níveis pressóricos e glicêmicos predizem mortalidade cardiovascular enquanto que a presença da Síndrome Metabólica não foi preditora de evento [6]. Nesse sentido, é crescente a discussão sobre a real importância clínica da identificação dessa Síndrome, e cada vez mais demonstrado o papel dos seus componentes individuais.

Essa tese reúne 3 estudos relacionados que foram desenvolvidos para uma maior compreensão do papel da homeostase pressórica nas complicações crônicas do Diabetes Melito

tipo 2 e Síndrome Metabólica. Os dois estudos iniciais foram desenvolvidos no Serviço de Endocrinologia do Hospital de Clínicas de Porto Alegre como parte de uma linha de pesquisa em homeostase pressórica e complicações crônicas do Diabetes Melito iniciada há mais de 2 décadas e chefiadas pelo Prof. Dr Jorge Gross; o terceiro estudo foi desenvolvido na University of California, San Diego através de intercâmbio internacional subsidiado pela CAPES – Programa de Doutoramento do País com Estágio no Exterior (outubro 2008 – setembro 2009).

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CAPÍTULO 1

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

Short running title: White-coat hypertension and diabetes

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Abstract

Objective: To determine the impact of white-coat hypertension (WCH) on microvascular complications in type 2 diabetes mellitus (DM).

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

Results: Forty-six type 2 DM patients had WCH (14.4%; age 56.6; 45.3% men) and 117, normotension (36.6%; age 55.8; 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 BP loads were higher in WCH subjects than in the normotensive ones. WCH was associated with an increased risk for macroalbuminuria (OR 4.9, 95%CI 1.3-18.7, P=0.01). On multivariate analysis models, WCH was associated with macroalbuminuria (OR 2.0 95%CI 1.3-3.2, P=0.02) and increased the risk for both non-proliferative and proliferative DR (OR 2.7, 95%CI 1.2-6.6, P=0.02 for any degree of DR) after adjustments for confounding factors.

Conclusions: Type 2 DM patients with WCH have an increased risk for DR and DN. Therefore, WCH should not be considered a harmless condition and treatment should be considered.

Introduction

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

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

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

Study Design and Methods

Patients

A cross-sectional study was performed with normotensive (n = 117) and WCH patients (n = 46) selected from a cohort of 319 type 2 DM patients regularly attending the DM outpatient clinic at Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, since 1994. Normotension was defined by an office BP <140/90 mmHg on at least two occasions during a 6-month period and daytime BP means on ABPM <135/85 mmHg; WCH was defined by an

office BP ≥140/90 mmHg on at least two occasions during a 6-month period and daytime BP means in ABPM <135/85 mmHg. None of the patients were on antihypertensive medications at the time of evaluation and those who were using any drug with anti-hypertensive effect had the medication suspended one week before the evaluation. Patients with serum creatinine >1.5 mg/dl, other renal diseases, cardiac arrhythmia, the presence of 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, and written informed consent was obtained from all patients.

Clinical Evaluation

Patients underwent an interview and clinical examination to record demographic and anthropometrical data, as previously described (7).

BP evaluations were performed 1 week after withdrawal of all medications with an antihypertensive effect. The analyses were performed based on the mean of two office BP values (measured with a mercury sphygmomanometer using 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 numbers 207/024751 and 207/038016 with calibration certification), with a 15-minute interval in the daytime and 20-minute 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 BP were recorded, as well as systolic and diastolic BP loads (percentage of 24-h and daytime BP ≥140/90 mm Hg and nighttime ≥120/80 mm Hg) and pulse pressure (systolic minus diastolic BP). The difference between the office

systolic BP and daytime systolic BP means was included in the analysis and described as the "white-coat effect".

BP was evaluated during exercise in a subset of patients (normotension: n = 38 and WCH: n = 18), by exercise treadmill test (standard Bruce protocol utilizing a computerized database) (8). Midway through each stage of the exercise protocol, at peak exercise and at one, two and four minutes after cessation of exercise, data on symptoms, heart rate and rhythm, BP and estimated workload (based on standards tables) in metabolic equivalents (METs: 1 MET equal 3.5 ml of oxygen uptake per kilogram of body weight per minute) were collected. The BP increment was defined as the difference between the peak exercise BP and resting BP.

Laboratory Methods

The urinary albumin excretion rate (UAER) was measured (values expressed in µg/min) by immunoturbidimetry [MicroAlb Sera-Pak® immuno microalbuminuria; Bayer, Tarrytown, NY on Cobas Mira Plus (Roche®); mean intra-assay and interassay CVs of 4.5 and 7.6 %, respectively] in at least two 24-h collections over the preceding 6 months (9). A1C test was measured by the 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 Jaffé method and serum total cholesterol and triglycerides were measured by enzymatic-colorimetric methods (Merck Diagnostica, Darmstadt, Germany; Boeringher Mannheim, Buenos Aires, Argentina), HDL cholesterol by homogeneous direct method (autoanalyzer, ADVIA 1650). LDL cholesterol was calculated using the Friedewald formula.

Outcomes

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

Diabetic nephropathy (DN): UAER was measured in 24-hour 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 (MDRD) Study: $186x[(\text{serum creatinine})^{-1.154}x(\text{age})^{-0.203}x(0.742, \text{ if female})x(1.210, \text{ if African descendant})]$ (11).

Statistical analysis

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

Results

WCH was found in 46 (14.4%; mean age 56.6; 45.3% men) and normotension in 117 (36.6%; mean age 55.8; 37.5% men) type 2 DM patients of the overall cohort. These groups were not different regarding age, DM duration, anthropometric characteristics, renal function,

glycemic control or lipid profile (Table 1). Interestingly, there were more active smokers among the normotensives than WCH patients.

The twenty-four-hour systolic BP means in ABPM were higher in WCH than in the normotensive group (124.7 ± 6.7 vs. 121.0 ± 8.5 mmHg, P = 0.01). Daytime systolic BP (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 BP loads (24-h, daytime and nighttime) followed the same pattern (Table 2).

White-coat hypertension and microvascular complications

UAER was higher in WCH in comparison with normotensive patients [15.5 (45.3) vs. 7.4 (15.2) μg/min, P = 0.01]. Moreover, the proportion of micro- and macroalbuminuric patients was higher in the WCH (normoalbuminuria: 57.1%, microalbuminuria: 28.6% and macroalbuminuria: 14.3%), when compared with 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 (OR 4.9 95%CI 1.3-18.7, P = 0.01), but not for microalbuminuria (Figure 1). This association was sustained after adjustments for DM duration and A1c test in the multivariate regression model (OR 2.0 95%CI 1.3-3.2, P=0.02).

Similarly, a higher prevalence of DR was found in WCH compared with normotensive patients (57.9% vs. 34.4%, P = 0.01). The presence of WCH increased the risk for both non-proliferative and proliferative DR (Figure 1). Moreover, WCH increased 2.7-fold (95%CI 1.2-6.6) the chance for any degree of DR after adjustment for DM duration and A1c test (P = 0.02). Including current smoking habit on multivariate regression models (for both UAER and DR 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 BP and daytime systolic BP 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 DM duration and A1c test (standardized beta coefficient 0.197, $P = 0.03$). Additionally, patients with proliferative DR ($n = 26$) presented with higher "white-coat effect" values [13 mm Hg (26)] than those without DR or non-proliferative DR [3 mm Hg (21), $P = 0.04$].

White-coat hypertension and response to exercise

Thirty-eight normotensives and 18 WCH patients performed exercise testing. The WCH group reached higher BP 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 groups, demonstrating equivalent effort during the test (Table 3).

Discussion

In this sample of type 2 DM subjects the prevalence of WCH was 14%. The clinical-laboratory characteristics of these subjects did not differ from the normotensive group, but higher BP levels were demonstrated during both the ABPM and exercise test. The presence of WCH increased the risk for DR 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 DR.

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 DM, reaching up to 74% in hypertensive type 1 (15) and 51% in type 2 DM patients (16). Subsequently, these findings were challenged in type 2 DM patients. Nielsen et al (17), found 23% WCH prevalence in normoalbuminuric individuals, 8% in microalbuminuric, and 9% in macroalbuminuric patients. The overall prevalence of 14% in type 2 DM patients of this study is the same as found in the general population, and closer to the Nielsen et al data (17). Differences concerning the definition of WHC (systolic/diastolic 24-h BP means or daytime systolic/diastolic BP means) might have contributed to some of the disparities between the studies. Moreover, the prevalence of WCH changes according to age, gender and ethnicity.

WCH has been historically treated as a benign phenomenon, since previous studies have demonstrated a lower risk for adverse events in this group than in 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 found similar clinical characteristics between WCH and normotensive individuals (22), while others have described a higher cardiovascular risk profile in WCH subjects (23; 24). Of interest is that current smoking habit was more frequent on normotensive group. This could reflect a life style change in subjects considered to be sicker, since they have increased levels at office. However, analyzing other vascular risk factors such as dyslipidemia, obesity, glycemic control, abdominal circumference no difference was observed between groups. Even in the absence of a worse risk profile, WCH was associated with DR and DN. To the best of our knowledge, this is the first study to report an association between WCH and microvascular complications in type 2 DM patients.

The higher BP peak demonstrated during the exercise test could be one example of how the BP responds to daily stressors in WCH subjects. 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 BP levels could lead to glomerular and retinal damage. Patel *et al* demonstrated increased retinal flow following a raise in BP in DM patients, suggesting that acute changes in BP have deleterious impact on retinal vessels (25). It is worth noting that all of the BP loads in WCH patients in our sample were higher than in the normotensive individuals, suggesting acute and repeated rises in BP 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 conclusion, WCH type 2 DM patients have an increased risk for microvascular complications. These findings indicate that WCH is not a benign situation in type 2 DM patients, most likely representing an intermediary phenotype between normotension and hypertension. Randomized controlled trials are needed to clarify the role of WCH treatment in preventing type 2 DM-associated complications.

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Table 1. Clinical and laboratory characteristics according to blood pressure classification

	Normotension (n = 117)	**White-coat hypertension (n = 46)**	**P**
Male subjects – n (%)	53 (45.3)	17 (37.5)	0.38
Age (years)	56.6 ± 10.2	55.8 ± 9.6	0.65
Diabetes mellitus duration (years)	9.8 ± 7.9	10.9 ± 7.0	0.38
Body mass index (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 – n (%)	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
High density cholesterol (mg/dl)	48.2 ± 13.1	47.8 ± 10.1	0.87
Low density cholesterol (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/1.73 m^2)	90.8 ± 24.4	92.9 ± 23.9	0.63

Table 2. Blood pressure characteristics according to blood pressure classification

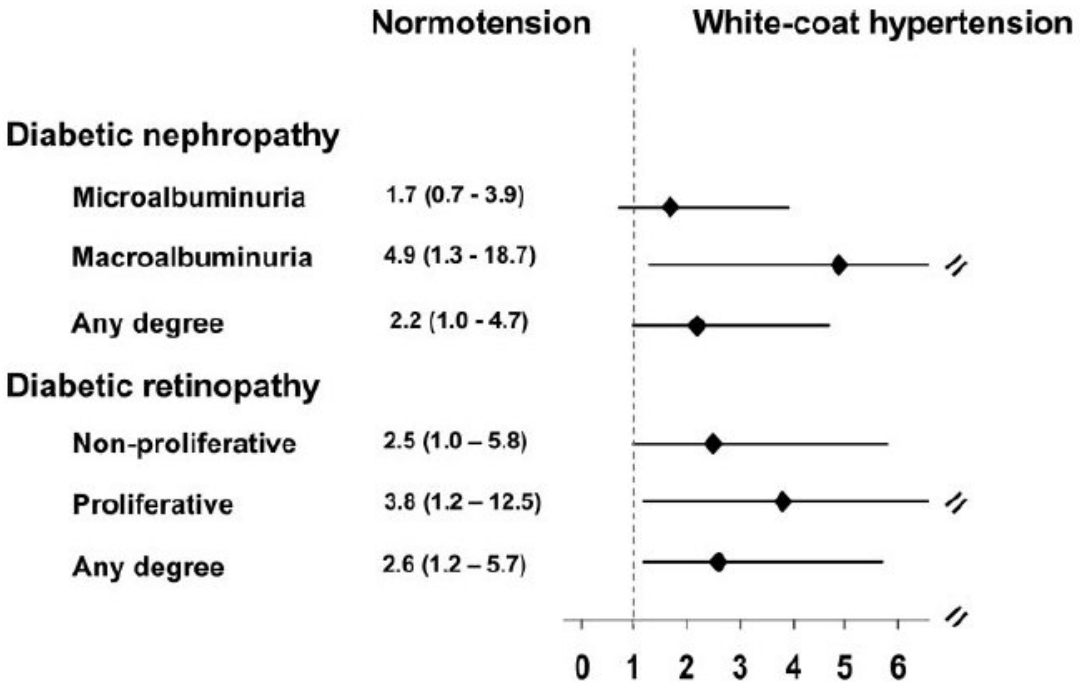
	Normotension (n = 117)	**White-coat hypertension** (n = 46)	**P**
Office			
Systolic blood pressure (mm Hg)	123.5 ± 10.8	149.7 ± 11.7	NA
Diastolic blood pressure (mm Hg)	75.9 ± 7.3	88.5 ± 9.2	NA
Pulse pressure (mm Hg)	47.5 ± 9.2	61.1 ± 13.8	<0.001
24-h			
Systolic blood pressure (mm Hg)	121.0 ± 8.5	124.7 ± 6.7	0.01
Diastolic blood pressure (mm Hg)	72.4 ± 6.0	72.7 ± 6.2	0.76
Pulse pressure (mm Hg)	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 (mm Hg)	123.2 ± 8.2	126.6 ± 7.2	0.01
Diastolic blood pressure (mm Hg)	74.8 ± 6.4	74.8 ± 7.0	0.97
Pulse pressure (mm Hg)	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 (mm Hg)	116.6 ± 11.8	119.8 ± 9.5	0.07
Diastolic blood pressure (mm Hg)	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 expressed as the mean ± SD or median (interquartile range).

Table 3. Blood pressure response to exercise according to blood pressure classification

	Normotension (n = 38)	**White-coat hypertension (n = 18)**	**P**
Resting Systolic Blood Pressure (mm Hg)	122.5 ± 15.3	130.6 ± 13.3	0.05
Resting Diastolic Blood Pressure (mm Hg)	77.8 ± 7.1	81.1 ± 6.7	0.11
Systolic Blood Pressure Increase (mm Hg)	44.3 ± 18.8	53.1 ± 18.5	0.10
Diastolic Blood Pressure Increase (mm Hg)	-1.3 ± 8.2	0.44 ± 7.7	0.43
Maximum Systolic Blood Pressure (mm Hg)	166.8 ± 16.1	183.7 ± 22.2	0.002
Maximum Diastolic Blood Pressure (mm Hg)	76.4 ± 8.1	81.5 ± 7.3	0.02
Total Metabolic Equivalent	8.1 ± 2.2	7.4 ± 1.5	0.24
Resting Heart Rate (bpm)	84 ± 13.3	88.1 ± 10.4	0.26
Peak Exercise Heart Rate (bpm)	154.9 ± 17.7	160.5 ± 13.2	0.23

Figure 1. White-coat hypertension odds ratio for type 2 diabetes mellitus chronic complications.



ANEXO 1

Impact of White-coat Hypertension on Microvascular Complications in Type 2 Diabetes Mellitus – Response to Kramer et al

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Carta comentário publicada no *Diabetes Care* 32:e24, 2009

In their recent study, Kramer et al. (1) performed a cross-sectional study comparing type 2 diabetes with whitecoat hypertension (WCH) and normotension and showed that type 2 diabetic patients with WCH have an increased risk for diabetic retinopathy and nephropathy. The results of their study point to the possibility that an acute rise in blood pressure levels in daily life has a deleterious impact on renal and retinal vessels. The findings of this study are important because the data have been scarce regarding the use of 24-h ambulatory blood pressure monitoring (ABPM) in diabetic patients. The authors discussed the possibility that acute rise in blood pressure due to daily stressors in patients with WCH could lead to microvascular damage because the WCH groups had a higher blood pressure peak during the exercise test. However, this can be interpreted differently: small artery remodeling (microvascular damage) can augment blood pressure surge by pressor stimulus (2). As cardiac output increases as a result of some stressors, blood pressure increases exponentially if there is a narrowing of small vessels. The coexistence of WCH and diabetes is hypothesized to be "prehypertension" (2) because it may reflect status of subclinical vascular damage. With regard to WCH and diabetes, we reported that diabetic WCH was not innocent of microvascular damage in the brain (3). We performed brain magnetic resonance imaging and ABPM on 360 Japanese hypertensive patients (226 women; average age 67 years), of whom 159 also had diabetes. Participants with diabetes and WCH had more silent cerebral infarctions (SCIs) (average 2.8 per person), whereas those with sustained hypertension but with no diabetes had an average of 2.3 silent strokes per person. Patients with diabetes and sustained hypertension had the most SCIs (average 5.2), whereas patients with WCH and no diabetes had the fewest SCIs (average 1.4). Hypertension- related microvascular damage was more advanced in diabetic patients, even in those with relatively lower blood pressure. The result is consistent

with the findings of Kramer et al. that diabetic WCH has more advanced target organ damage than nondiabetic WCH and that blood pressure control is important even in the context of a transient rise in blood pressure. We have, in a previous study (4), discussed the concept of "white-coat hypertension syndrome," defined as WCH and metabolic abnormalities, which are characteristics of insulin resistance; the increased risk of target organ damage is determined not only by blood pressure but also by metabolic abnormality in these patients. Even in the case of transient elevation of blood pressure in WCH, the existence of a white-coat effect would be associated with target organ damage. On the other hand, we have recently shown that cardiovascular prognosis of diabetic WCH was not as bad as that associated with sustained hypertension in diabetes and that it was even similar to that of nondiabetic WCH during 4 years of follow-up (5). The results of this study imply that blood pressure must be continuously rather than transiently elevated in order to cause cardiovascular events.

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ANEXO 2

Impact of White-coat Hypertension on Microvascular Complications in Type 2 Diabetes Mellitus – Response to Eguchi et al

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Carta resposta publicada no *Diabetes Care* 32:e25, 2009

Eguchi et al pointed out that microvascular damage associated with white-coat hypertension (1) may be the cause of increased blood pressure responses to daily stressors. This is a very interesting and original interpretation, but the direction of the cause and effect relation between microvascular disease and blood pressure response to exercise can only be confirmed by prospective cohort studies. We share Dr Eguchi's idea that continuously high levels of blood pressure are more important for the development of diabetic complications than transient rises. In a previous study of our group, Leitão et al studied 270 type 2 diabetes mellitus (DM) patients with ambulatory blood pressure monitoring (ABPM), and have verified that the correlations between urinary albumin excretion rate and echocardiography structural alterations with 24-h systolic blood pressure means were more consistent and of greater magnitude than with night/day blood pressure ratios (2). Reinforcing the role of sustained hypertension, Leitão et al demonstrated that type 2 DM patients with masked hypertension (office normotension but hypertension on ABPM) had higher albumin excretion and increased left ventricular wall thickness than truly normotensives (3). Given the current evidence on ABPM and type 2 DM complications, we believe that blood pressure levels are a strong predictor of chronic complications, and blood pressure should not be categorized only as normal or abnormal, but rather taking into account the even subtle changes in blood pressure homeostasis, such as masked hypertension (3), white-coat hypertension (4), and high normal blood pressure levels (5).

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CAPÍTULO 2

Late afternoon blood pressure increase is associated with diabetic retinopathy in normotensive type 2 diabetes mellitus patients

Short running title: Late afternoon blood pressure and diabetic retinopathy

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Abstract

Aims: To identify if the variability of blood pressure (BP) is associated with diabetic retinopathy (DR) in normotensive type 2 DM patients.

Methods: Sixty-five normotensive type 2 DM patients that had 24-h ambulatory BP monitoring (ABPM) were grouped according any degree of DR.

Results: Fourteen (21%) patients had DR. Office BP and 24-h BP parameters did not differ between groups. At late afternoon period, patients with DR had higher increment in both systolic (11.3 ± 12.7 vs. 1.0 ± 11.4 mm Hg, P = 0.006) and diastolic (6.7 ± 8.6 vs. -0.73 ± 10.0 mm Hg, P = 0.017) BP levels than those without. Multivariate logistic analyses were performed with DR as a dependent variable. Each 1 mm Hg increment in systolic BP at the late afternoon period was associated with a 10.2% increase in DR prevalence [OR 1.102 (CI 95% 1.011-1.202, P = 0.027)], after adjustments for A1C test, DM duration, age, albuminuria and current smoking.

Conclusions: In conclusion, in normotensive type 2 DM patients, BP increase at late afternoon is associated to DR independently from confounder factors or other ABPM parameters.

Keywords: type 2 diabetes mellitus, late afternoon, blood pressure variability, diabetic retinopathy

Introduction

Hypertension is the main risk factor for diabetic retinopathy (DR) (1; 2) but DR can be found in a significant proportion of office normotensive DM patients (3). Experimental models have suggested that alterations in BP variability in normotensive range are associated with retinal damage (4), suggesting that instability of BP patterns, such as abnormal increments, could lead to retinal damage, even in normotensive patients. Therefore we investigated if increased BP variability along the day is associated with DR in normotensive type 2 DM patients.

Research Design and Methods

A cross-sectional study was performed in type 2 DM patients (5). Normotensive patients (n = 65) were selected from a cohort of 270 type 2 DM (6). Normotension was defined by ambulatory BP <140/90 mm Hg and daytime mean BP levels on ambulatory BP monitoring (ABPM) <135/85 mm Hg. None of the patients were on antihypertensive medications, have serum creatinine above 1.5 mg/dL or cardiac disease. ABPM was performed by oscillometry. The BP variation in 4-hour period was assessed (maximum minus minimum BP value).

Clinical and laboratorial evaluation was performed as previous described (7). Fundus eye examination was performed by an ophthalmologist and patients were grouped as absence or any degree of DR (8).

Student t test was performed as appropriate. To compare BP changes between groups, analysis of variance for repeated measures was also performed.

Results

Fourteen patients (21.5%) had any degree of DR. Patients with DR had higher total cholesterol (223 ± 44 vs. 183 ± 36 mg/dl, P = 0.003) and LDL values (135 ± 27 vs. 102 ± 29

mg/dl, P = 0.002) than those without DR. Age (53.3 ± 9.3 vs. 54.3 ± 11.8 years, P = 0.99), DM duration (10.53 ± 3.99 vs. 7.64 ± 5.41 years, P = 0.90), albuminuria [10 (3.8-202) vs. 8.6 (0.1-1143) µg/min, P = 0.33], body mass index (28.8 ± 2.9 vs. 28.8 ± 4.6 kg/m^2, P = 0.64), waist circumference (94 ± 8.5 vs. 97 ± 9.8 cm, P = 0.46), glycemic control (fasting glucose: 195 ± 121 vs. 152 ± 46 mg/dL; A1c test: 7.6% ± 1.9 vs. 6.6% ± 2, P = 0.17) and smoking habit were not different between groups.

Office BP did not differ between groups (systolic: 122 ± 11 vs. 123 ± 9 mm Hg, P = 0.666; diastolic: 74 ± 6.7 vs. 77 ± 7.5 mm Hg, P = 0.251), as well as 24-h BP (systolic: 121.3 ± 6.5 vs. 119.3 ± 6.4 mm Hg, P = 0.338; diastolic: 72.8 ± 5.7 vs. 72.5 ± 5.6 mm Hg, P = 0.880), daytime (systolic: 123 ± 5.1 vs. 121.9 ± 6.3 mm Hg, P = 0.572; diastolic: 74.3 ± 5.7 vs. 75.5 ± 5.7 mm Hg, P = 0.548) and nighttime BP (systolic: 119.3 ± 11.6 vs. 112.9 ± 8.1 mm Hg, P = 0.890; diastolic: 69 ± 7.5 vs. 65.7 ± 7.21 mm Hg, P = 0.172).

Analyzing the BP variation during the day (Table 1), patients with DR had a higher increment in both systolic (11.3 ± 12.7 vs. 1.0 ± 11.4 mm Hg, P = 0.006) and diastolic (6.7 ± 8.6 vs. -0.73 ± 10.0 mm Hg, P = 0.017) BP levels at the late afternoon period (4 to 8 P.M.) than those without. Conversely, at early morning (4 to 8 A.M) BP variation was decreased in patients (with DR) (systolic: 3.8 ± 13.4 vs. 15.4 ± 15.9 mm Hg, P = 0.019; diastolic: 5.1 ± 8.5 vs. 15.2 ± 11.5 mm Hg, P = 0.004).

On analysis of variances for repeated measures, systolic BP variation between 4 to 8 P.M. (P = 0.045) and 4 to 8 A.M. (P = 0.015) were different between groups. However, for diastolic BP, variation differed only in 4 to 8 A.M. period (P = 0.012) (Figure 1).

As the differences in DR prevalence could be due to higher absolute BP levels at the late afternoon and nighttime period rather than its rise, the BP mean values between 4 P.M. to 8

A.M were compared. There were no differences in systolic (117.3 ± 10.7 vs. 122.0 ± 8.2 mm Hg, P = 0.118) or diastolic (71.7 ± 6.2 vs. 69.9 ± 8.1 mm Hg, P = 0.448) values between groups.

Multivariate logistic analyses were performed with DR as a dependent variable. For each 1 mm Hg in systolic BP variation at late afternoon (4 to 8 P.M) [OR 1.102 (CI 95% 1.011-1.202, P = 0.027)] an increase of 10.2% in DR prevalence was observed after adjustments for A1c test, DM duration, age, albuminuria and current smoking. Other regression models were constructed replacing BP variation at late afternoon by others 4-hour periods (table 2). None of them were associated with DR. Including lipid profile on multivariate analysis did not change any of the results.

Conclusion

In this sample of normotensive type 2 DM patients, increased BP at late afternoon period, during the 24-h ABPM, was associated with DR after adjustments for known risk factors.

In non-DM patients, BP circadian rhythm is characterized by a morning rise, daytime *plateau* and a nocturnal decrease of at least 10% of daytime mean BP levels (9). In this sample, a significant BP increase was observed at late afternoon in normotensive patients with DR. Interestingly, mean 24-h, nighttime and late afternoon plus nighttime BP levels were not different between groups, suggesting that, especially in normotensive subjects, acute BP rise can have important role in DR development.

Patel *et al*, demonstrated an increase in retinal flow after rising BP in setting of hyperglycemia which included DM patients, suggesting that acute changes in BP have deleterious impact on retinal vessels (10). Retinal vascular auto regulation broke down with an

increase of 30% in BP in normoglycemic and 15% in hyperglycemic DM patients and 40% in normal individuals. In our sample, a mean increase of approximately 10% in systolic BP levels at late afternoon was already associated with DR.

One limitation of this report is the cross-sectional design that precludes a causal relation between late afternoon BP variability and DR development. However, this limitation does not obscure the main results of this study.

In conclusion, in normotensive type 2 DM patients, BP increase at late afternoon is associated to DR independently from confounder factors or ABPM parameters. The evaluation of normotensive type 2 DM patients with ABPM and its detailed analysis, with special attention to the late afternoon period, might be important to identify a high-risk group for DR. Larges studies focusing BP variability in type 2 DM patients are needed in order to confirm these findings and plan prevention and treatment interventions in patient at risk for DR.

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Table 1. Blood pressure variation during 24-h ambulatory monitoring of blood pressure

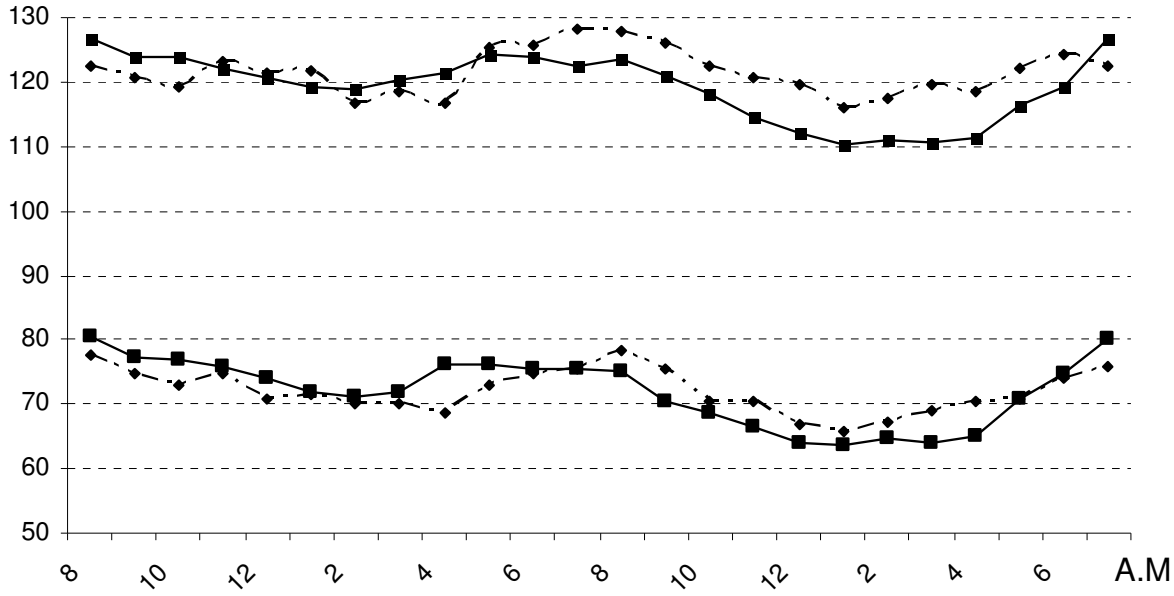
	Diabetic Retinopathy		
	Absent (n = 51)	**Present (n = 14)**	**P**
Systolic blood pressure variation (mm Hg)			
8 to 12 A.M.	-4.5 ± 9.6	0.6 ± 9.3	0.084
12 to 4 P.M.	-0.3 ± 11.5	-3.0 ± 9.3	0.434
4 to 8 P.M.	1.0 ± 11.4	11.3 ± 12.7	0.006
8 to 12 P.M.	-9.1 ± 12.8	-7.3 ± 21.3	0.690
12 to 4 A.M	1.4 ± 12.1	0.1 ± 12.6	0.736
4 to 8 A.M	15.4 ± 15.9	3.8 ± 13.4	0.019
Diastolic blood pressure variation (mm Hg)			
8 to 12 A.M	-4.5 ± 9.8	-2.9 ± 3.7	0.339
12 to 4 P.M.	-2.3 ± 9.6	-0.5 ± 8.3	0.533
4 to 8 P.M.	-0.73 ± 10.0	6.7 ± 8.6	0.017
8 to 12 P.M	-8.5 ± 10.0	-7.8 ± 15.6	0.831
12 to 4 A.M	-0.01 ± 8.9	-2.0 ± 9.2	0.479
4 to 8 A.M	15.2 ± 11.5	5.1 ± 8.5	0.004

Table 2. Multivariate analysis of blood pressure variability and the presence of diabetic retinopathy in normotensive Type 2 Diabetes*

	OR	CI (95%)	P
Systolic blood pressure variation (mm Hg)			
8 to 12 A.M.	1.02	0.9-1.1	0.63
12 to 4 P.M.	0.94	0.82-1.08	0.43
4 to 8 P.M.	1.10	1.01-1.2	0.02
8 to 12 P.M.	0.97	0.88-1.07	0.57
12 to 4 A.M	0.98	0.86-1.12	0.80
4 to 8 A.M	0.90	0.80-1.1	0.30
Diastolic blood pressure variation (mm Hg)			
8 to 12 A.M	0.87	0.72-1.06	0.18
12 to 4 P.M.	0.94	0.78-1.13	0.53
4 to 8 P.M.	1.23	1.01-1.48	0.03
8 to 12 P.M	0.95	0.87-1.04	0.30
12 to 4 A.M	0.93	0.81-1.08	0.38
4 to 8 A.M	0.78	0.73-1.01	0.06

* Adjusted for A1c test, diabetes mellitus duration, age, albuminuria and current smoking

Figure 1. Systolic and diastolic blood pressure variation during 24-h ambulatory blood pressure monitoring according to presence (open line) or absence (continuous line) of diabetic retinopathy



CAPÍTULO 3

Blood Pressure and Fasting Plasma Glucose rather than Metabolic Syndrome Predict Coronary Artery Calcium Progression: The Rancho Bernardo Study

Running title: Blood pressure & glucose predict CAC progression

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Abstract

Objective: To examine the association of the metabolic syndrome (MetS), defined by WHO and ATP-III criteria, and its components with coronary artery calcium (CAC) progression.

Research Design and Methods: Participants were 338 older community-dwelling men and women without known heart disease who had measurements of heart disease risk factors and coronary artery calcium (CAC) at 2 clinic visits with an average interval of 4.5 years. Progression was defined as an increase in total CAC volume score ≥2.5 mm^3.

Results: At baseline mean age was 67.6 years; MetS was present in 15.1% by WHO criteria and 11.8% by ATP-III criteria; 5.3% met both criteria. Participants with WHO-defined MetS had a greater change in total CAC volume score than those without (P = 0.001). There was no significant difference in CAC volume change by ATP-III-defined MetS status (P = 0.69). Overall 46.4% of participants were CAC progressors. In logistic regression analyses adjusted for age, sex, smoking status, and low density lipoprotein cholesterol, neither WHO nor ATP-III defined MetS predicted CAC progression. Among MetS components, only hypertension was independently associated with CAC progression (OR 2.11 95% CI 1.33-3.3x, P = 0.002). Fasting blood glucose (>100 mg/dL) was an independent predictor of CAC progression, but only for the 118 participants younger than age 65 (OR 2.3 95% CI 1.01-5.5, P = 0.04).

Conclusions: In older adults without known heart disease, blood pressure levels and fasting plasma glucose were better independent determinants of CAC progression than MetS itself.

Keywords: metabolic syndrome, atherosclerosis, coronary artery calcium

Introduction

Coronary artery calcium (CAC) assessed by electron-beam computed tomography (CT) is a marker of atherosclerotic plaque burden (1) and predicts future cardiac events independent of traditional coronary heart disease (CHD) risk factors (2; 3). Moreover, CAC progression is associated with worsening of plaque burden as assessed by angiography (4). An increase of more than 15% in the total CAC score predicts an increased risk of myocardial infarction in observational studies (1; 5; 6).

Population-based studies using either World Health Organization (WHO)-defined metabolic syndrome (MetS) or National Cholesterol Education Program Adult Treatment Panel III criteria (ATP-III) have shown that mortality from coronary heart disease (CHD) is higher in people with MetS (7; 8). In cross-sectional studies MetS has been associated with greater CAC burden (8-10), and one study found that MetS components such as hypertension and diabetes mellitus were independent predictors of CAC progression (11), but the effect of MetS on CAC progression has not been reported.

We examined the prevalence of MetS defined by WHO and ATP-III criteria in older community-dwelling, ambulatory adults without known CHD, and the independent association of baseline MetS or its components with CAC progression in this cohort.

Research Design and Methods

Study population

Participants were members of the Rancho Bernardo Study, a southern California community-based study of middle to upper-middle class Caucasian adults established in 1972. This paper examines the surviving community-dwelling participants with no history of CHD (angina pectoris, myocardial infarction, or coronary artery revascularization) who participated

in a clinic visit in 1997-1999 and returned for a follow-up visit in 2005-2006 (mean interval 4.5 ± 0.5 years). At the 1997-99 visit 422 participants had electron beam CT of the heart to test for coronary artery calcification; 342 returned for the follow up evaluation. Reasons for not returning (n = 84) included refusals (n = 43), deaths (n = 21), and participants who were unreachable or cancelled their appointment for unknown reasons (n = 20). In addition, 4 participants completed the second visit but refused blood draw and were excluded, leaving 338 participants for the present analyses. Compared to the participants who returned, those who did not return were older and had higher levels of systolic blood pressure and fasting plasma glucose at the baseline visit, but did not differ in other risk factors. All participants provided written informed consent at both visits. The study protocol was approved by the Human Research Protection Program at the University of California, San Diego.

Data collection

In 1997-1999, height and weight were measured in participants wearing light clothing and no shoes, using a regularly calibrated scale and stadiometer. Body mass index (BMI) was calculated as weight (kilograms)/height^2 (meters). Waist circumference was measured in standing subjects midway between the inferior lateral margin of the ribs and the superior lateral border of the iliac crest. Hip circumference was measured as the widest hip circumference.

Fasting plasma glucose and high- and low-density lipoprotein cholesterol (HDL-c and LDL-c) levels were measured in a Lipid Research Clinic laboratory using standard enzymatic methods in blood samples collected after an overnight, usually 12-hour, fast. Systolic and diastolic blood pressures were measured twice in seated resting subjects by certified staff according to a standard protocol (12). Hypertension was defined as systolic blood pressure ≥140 and/or diastolic ≥90 mm Hg or use of anti-hypertensive medication. Other cardiovascular

risk factors including current cigarette smoking, alcohol intake (≥3 times/week), and physical activity (exercise ≥3 times/week) were assessed using standard questionnaires. Baseline medication use was validated by a trained nurse who examined pills and prescriptions brought to the clinic for that purpose; medication use at the time of the second CAC evaluation was obtained by questionnaire.

Metabolic syndrome (MetS) was defined in two ways, in accord with WHO criteria (13) or ATP-III guidelines (14). MetS by WHO criteria required type 2 diabetes, impaired fasting glucose (fasting glucose 110-125 mg/dL), or impaired glucose tolerance (postchallenge glucose 140-199 mg/dL) plus any two of the following: hypertension (≥140/90 mm Hg or use of anti-hypertensive drugs), high triglycerides (≥150 mg/dL), low HDL-c (<35 mg/dL for men and <39 mg/dL for women), obesity (BMI >30 kg/m^2 and/or waist/hip ratio >0.9 for men and >0.85 for women), urinary albumin excretion rate ≥20 μg/min or albumin/creatinine ratio ≥30 mg/g. MetS by ATP-III criteria required 3 or more of the following: fasting plasma glucose ≥110 mg/dL, abdominal obesity (male waist circumference >102 cm and female >88 cm), high triglycerides (≥150 mg/dL), low HDL-c (<40 mg/dL for males and <50 mg/dL for females), and hypertension (≥130/85 mm Hg or use of anti-hypertensive drugs).

CT-imaging protocol

CAC scores were assessed using electron-beam CT (Imatron C-150 scanner, Imatron, San Francisco, California). Heart images were obtained with 100-ms scan time using 3-mm slices starting at the level of the carina and proceeding to the level of the diaphragm; approximately 40 to 45 "slices" were obtained. Tomographic imaging was electrocardiographically triggered at 40% or 65% of the RR interval, depending on the participant's heart rate. CAC was defined as a plaque of ≥2 pixels (area 0.67 mm^2) with a

density ≥130 Hounsfield units (HU). Quantitative calcium scores were calculated using the method of Agatston and colleagues (15) and by volumetric scores (acquired by multiplying the pixel area by the section thickness of the region of interest). The total volume scores were derived by the sum of all lesion volumes in cubic millimeters.

Statistical analyses

All analyses were performed using SPSS (version 13.1, SPSS, Inc., Chicago, IL). In univariate analyses, clinical characteristics and MetS components were compared by presence of MetS by ATP-III or WHO criteria using Student t tests. P values <0.05 were considered significant. Variables with normal distribution were presented as means ± standard deviation (SD) and those with non-normal distribution as median and inter-quartile range. Skewed variables were log transformed for statistical analyses.

CAC scores were categorized according to the criteria of Rumberger (16), which define CAC scores of 0-10 HU as none/minimal, 11-99 HU as mild, 100-399 HU as moderate, and ≥400 HU as severe. CAC progression was analyzed as continuous outcome (CAC volume scores change = CAC volume score on second visit minus CAC volume score at baseline visit), and as categorical outcome (CAC progression yes/no). We defined progression as a difference between baseline CAC and follow-up square-root transformed total CAC volume score ≥2.5 mm^3 (17). Because interscan variability and error depend on CAC absolute value (CAC variability and score error are larger in patients with increased baseline CAC scores than in those with lower scores), this definition provides an estimate of change that is unbiased with respect to baseline CAC. In the present study this definition of CAC progression is between the mean and -1 standard deviation of square-root transformed CAC change, which is

approximately equivalent to an annual increase of 30% in CAC absolute values and concordant with previous studies that observed an annual 24% CAC increase in untreated adults (18).

The association between the presence of MetS or its individual components and total CAC volume score change was examined using linear regression before and after adjustment for potential non-MetS confounding variables (age, sex, smoking status, and LDL-c). These covariates were chosen based on established associations with CAC and atherosclerosis; highly correlated variables such as total cholesterol and LDL-c were not used in the same model. The Hosmer and Lemeshow test was applied to evaluate whether the estimates of the model fit the data at an acceptable level ($P > 0.05$). Individual risk factors were examined as predictors of categorical CAC progression in logistic regression models before and after adjustment for the same confounders. CAC progression analyses were repeated stratifying by age <65 and ≥65 years.

Results

Participants were 156 men and 182 women aged 67.6 ± 7.6 years. Mean follow up was 4.5 ± 0.5 yrs. The average (SD) body mass index was 26.2 (3.8) kg/m^2; mean total cholesterol was 208.1 (34) mg/dL; 43.5% were hypertensive; and 7.2% had diabetes mellitus. Half the cohort had never smoked and 5.3% were current smokers. Prevalence of MetS at baseline was 15.1% (44/292) by WHO criteria and 11.8% (40/338) by ATP-III criteria (the sample size was smaller for participants classified by WHO criteria because only 292 of the 338 participants were evaluated for baseline albuminuria). Only 18 of 292 subjects (5.3%) met both definitions of MetS. Table 1 shows prevalence of MetS components for participants with and without WHO- and ATP-III-defined MetS. By definition, participants with MetS by either criterion had increased conventional risk factors (blood pressure, fasting glucose, triglycerides, and low

HDL-c) as well as adverse anthropometric characteristics compared to those without. Total cholesterol and LDL-c were not associated with MetS by either definition.

Participants with WHO-defined MetS at baseline were more likely to be using a diuretic (25% vs. 9.7%, P = 0.04), cholesterol lowering medication (29.5% vs. 14.9%, P = 0.01), or calcium channel blocker (18.2% vs. 6.9%, P = 0.01) than those without MetS, and estrogen therapy was less common among women with MetS (13.2% vs. 41.9%, P = 0.03). There were no differences in the use of aspirin, β-blockers, or angiotensin converting enzyme inhibitors. More individuals with MetS by ATP-III criteria were using diuretics (27.5% vs. 9.7%, P <0.001) or β-blockers (27.5% vs. 6.7%, P <0.001) than those without MetS, but use of cholesterol lowering medications, calcium channel blockers, angiotensin converting enzyme inhibitors, aspirin, or estrogen therapy did not differ significantly.

Cross-sectional CAC score results and MetS defined by WHO and ATP-III

At the baseline visit, 37% of participants had none/minimal CAC, 21.6% mild, 19.5% moderate, and 21.9% severe CAC according to Rumberger category. Individuals with WHO-defined MetS were more likely to be in a more severe Rumberger category of CAC at the baseline visit than those without MetS (none/minimal CAC: 6.8% vs. 44%; mild: 15.9% vs. 22.6%; moderate: 31.8% vs. 16.5%; severe: 45.5% vs. 16.9%, P for trend <0.001). In contrast, the presence of MetS defined by ATP-III was not associated with CAC category at baseline (none/minimal CAC: 30% vs. 37.9%; mild: 25% vs. 21.1%; moderate: 20% vs. 19.5%; severe: 25% vs. 21.5%, P for trend 0.73). When prevalence of MetS components by both criteria and CAC categories were compared, only hypertension, impaired glucose metabolism, and obesity increased with CAC severity (see table 2).

The calcium volume score at baseline [median (interquartile-range)] was significantly higher among participants with MetS by WHO criteria [231.4 mm^3 (430)] when compared to participants without WHO MetS [25.3 mm^3 (155), P <0.001]. In similar comparisons between those with and without MetS defined by ATP-III criteria, there were no differences in CAC volume scores at baseline [71 (409) vs. 34 (201) mm^3, P = 0.34].

Changes in CAC volume score and MetS defined by WHO and ATP-III

Overall, 157 (46.4%) participants had significant CAC progression (change in square root volume score ≥ 2.5 mm^3) over the 4.5 yr follow-up. The increase in calcium volume score [median (interquartile-range)] was higher in participants with MetS by WHO criteria [102 mm^3 (227)] than in those without [22.9 mm^3 (85), P = 0.001)], however the proportion of CAC progressors did not differ (54.5% vs. 44%, respectively, P = 0.19). Comparing CAC changes between those with and without MetS by ATP-III criteria, neither the absolute change [21 mm^3 (118) vs 31 mm^3 (110), P = 0.69] nor the proportion of CAC progressors (45% vs. 46.6%, P = 0.84) were significantly different.

Multivariate analysis

Multivariate linear regression was used to assess the association between CAC volume score change and individual components of MetS as continuous variables adjusting for age, sex, LDL-c, and smoking status. Only blood pressure (standardized beta coefficient systolic blood pressure: 0.19, P = 0.001; diastolic 0.14, P = 0.007) and fasting plasma glucose (standardized beta coefficient 0.16, P = 0.02) were independently associated with CAC progression (Table 3). The same multivariable model was used to assess the association between MetS by WHO or ATP-III criteria with categorical (yes/no) progression of CAC. Neither MetS by WHO nor ATP-III was associated with CAC progression in age, sex, LDL-c,

and smoking status adjusted models (Figure 1). Of the individual components, only hypertension was associated with CAC progression (OR 2.11 95%CI 1.33-3.3, P = 0.002) (Figure 1). Moreover, CAC volume changes were greater for higher categories of systolic blood pressure [CAC volume change (square root): 1.8 ± 2.2 for systolic BP <120 mm Hg, 2.4 ± 2.8 for 120-140 mm Hg, 3.1 ± 3.2 for 140-160 mm Hg, 4.1 ± 3.0 for >160 mm Hg, P = 0.003 for linear trend] in models adjusting for the same covariates.

In a post-hoc analysis stratified by age group, fasting hyperglycemia (>100 mg/dL) was an independent predictor of CAC progression (OR 2.3 95%CI 1.01-5.5, P = 0.04) for participants younger than 65 years old (n = 118), but not for the older group. Age-stratified analyses did not differ for other MetS components or for the presence of the MetS. Further adjustment for medication use did not materially change any of the results.

Conclusion

The prevalence of MetS in this older Caucasian population without known CHD was 11-13% depending on MetS definition; MetS by either definition was not an independent predictor of CAC progression. Among the MetS components, only hypertension was independently associated with CAC change overall, while hyperglycemia independently predicted CAC progression only in individuals younger than age 65.

The prevalence of the MetS in adult Caucasians in the United States is reported to be 20 to 25% (19). The lower prevalence in our cohort likely reflects the fact that persons with known CHD were excluded. This might have had the effect of reducing associations by exclusion of those with more risk factors who already had heart disease. This fits with the age- stratified analyses, where results were more pronounced in participants younger than age 65.

The finding that individuals with MetS by WHO criteria but not by ATP-III criteria had higher values of CAC at the baseline visit and more progression during follow up is concordant with a small study (100 men aged 30-39) in which MetS defined by WHO, but not ATP-III, was independently associated with CAC >10 HU (20). This study did not report CAC progression.

The main CHD risk factors reported to be associated with CAC progression are age, male sex, baseline CAC scores, diabetes, hypertension, and use of cholesterol-lowering medication (5; 6; 21). In the large (5756 participants) Multi-Ethnic Study of Atherosclerosis (MESA), which evaluated risk factors for CAC progression over 2.4 years, many cardiovascular risk factors (age, male sex, hypertension, body mass index, diabetes mellitus, and family history of heart attack) were associated with both the risk of developing incident CAC and increases in existing calcification (11). Compared to the present study, MESA was much larger, had a shorter interval between scans, and defined CAC progression as any newly detectable CAC, which may not allow a fair comparison. Moreover, MESA did not evaluate MetS as a predictor of CAC progression.

Based on new evidence, the usefulness of the MetS definition has been questioned. In a paper published after the present analysis was completed, based on a large cohort of 7258 adults 65 years or older free of CHD, MetS by either ATP-III or WHO definitions did not predict CHD mortality, but two components (blood pressure and glucose) did (22). These results parallel those in the present study, in which, after adjusting for confounders, blood pressure and glucose but not MetS were useful in predicting who will have progression of subclinical atherosclerosis. In our study, the presence of hypertension was associated with

110% increased likelihood of CAC progression, and its presence was a better predictor than the presence of MetS by WHO or ATP-III criteria.

In summary, WHO MetS was superior to ATP-III MetS in predicting subclinical atherosclerosis by CAC scores. When other classical heart disease risk factors were included, the presence of the MetS itself did not predict CAC progression, but two of its components, systolic blood pressure and fasting plasma glucose, were independently associated with CAC changes. These results highlight the importance of these reversible risk factors in older adults.

Disclosure: The Rancho Bernardo Study was funded by the National Institutes of Health/National Institute on Aging, grant AG07181 and grant AG028507 and the National Institute of Diabetes and Digestive and Kidney Diseases, grant DK31801. There are no conflicts of interest.

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Table 1. Baseline prevalence of WHO and ATP-III metabolic syndrome and their components in older adults without known cardiovascular heart disease

Metabolic syndrome defined by WHO criteria	**Yes (n = 44)**	**No (n = 248)**
Prevalence of WHO components (%)		
Impaired glucose metabolism [type 2 diabetes, impaired fasting glucose (110-125 mg/dL) or impaired glucose tolerance (140-199 mg/dL)]	100.0	5.2
Obesity (BMI >30 kg/m^2 and/or waist/hip ratio >0.9 for men and >0.85 for women)	97.7	55.2
High triglycerides (≥ 150 mg/dL)	56.8	25.8
Low HDL-c (<35 mg/dL for men and <39 mg/dL for women)	11.4	1.2
Hypertension (≥140/90 mm Hg or use of anti-hypertensive drugs)	84.1	37.1
Albuminuria (urinary albumin excretion rate ≥ 20 µg/min or albumin/creatinine ratio ≥ 30 mg/g)	9.1	2.8
Metabolic syndrome defined by ATP-III criteria	**Yes (n = 40)**	**No (n = 298)**
Prevalence of ATP-III components (%)		
Fasting plasma glucose >110 mg/dL	47.5	14.8
Abdominal obesity (waist circumference >102 for men and >88 cm for women)	72.5	14.1
High triglycerides (≥ 150 mg/dL)	80.0	22.5
Low HDL-c (<40 mg/dL for men and <50 mg/dL for women)	80.0	7.4
Hypertension (≥130/85 mm Hg or use of anti-hypertensive drugs)	90.0	51.7

Table 2. Prevalence of ATP-III and WHO metabolic syndrome and their components by CAC score category at baseline

Coronary artery calcium Score	**None/minimal (n = 125)**	**Mild (n = 73)**	**Moderate (n = 66)**	**Severe (n = 74)**	**P**
Prevalence of WHO components (%)					
Impaired glucose metabolism [type 2 diabetes, impaired fasting glucose (110-125 mg/dL) or impaired glucose tolerance (140-199 mg/dL)]	7.2	17.8	28.8	31.1	<0.001
Obesity (BMI >30 kg/m^2 and/or waist/hip ratio >0.9 for men and >0.85 for women)	40.0	68.5	71.2	82.4	<0.001
High triglycerides (≥ 150 mg/dL)	28.0	28.8	30.3	31.1	0.61
Low HDL-c (<35 mg/dL for men and <39 mg/dL for women)	0.8	2.7	6.1	4.1	0.08
Hypertension (≥140/90 mm Hg or use of anti-hypertensive drugs)	32.8	44.3	53	55.4	0.001
Albuminuria (urinary albumin excretion rate ≥ 20 µg/min or albumin/creatinine ratio ≥ 30 mg/g)*	4.5	1.6	3.6	4.8	0.90
Prevalence of ATP-III components (%)					
Fasting plasma glucose >110 mg/dL	7.2	17.8	27.3	31.1	<0.001
Abdominal obesity (waist circumference >102 for men and >88 cm for women)	17.6	20.5	19.7	28.4	0.10
High triglycerides (≥ 150 mg/dL)	28.0	28.8	30.3	31.1	0.61
Low HDL-c (<40 mg/dL for men and <50 mg/dL for women)	15.2	17.8	18.2	13.1	0.87
Hypertension (≥130/85 mm Hg or use of anti-hypertensive drugs)	40.8	61.6	66.7	67.6	<0.001

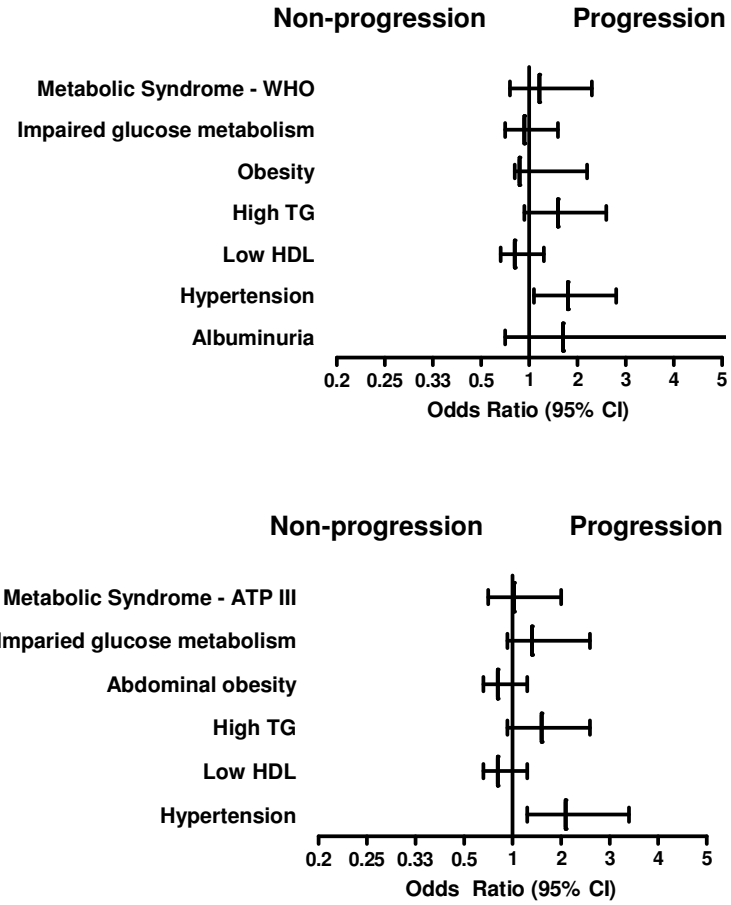
*total n = 292; none/minimal CAC, n= 112; mild CAC, n= 63; moderate CAC, n= 55; severe CAC, n= 62

Table 3. Standardized Beta coefficients for multivariate linear regressions of individual metabolic syndrome components and change in total coronary calcium volume score (square root)

	Standardized Beta coefficient*	**P value**
Metabolic syndrome components		
Fasting blood glucose (mg/dL)	0.16	0.02
Waist circumference (cm)	0.10	0.11
Waist/hip ratio	0.16	0.07
Body mass index (kg/m^2)	0.04	0.43
Triglycerides (mg/dL)	0.04	0.36
HDL-c (mg/dl)	0.06	0.29
Systolic blood pressure (mm Hg)	0.19	0.001
Diastolic blood pressure (mm Hg)	0.14	0.007
Albuminuria (mg/L)	0.05	0.38

*Adjusted for sex, age, current smoking status, and LDL-c

Figure 1. Adjusted* odds ratio for metabolic syndrome and metabolic syndrome components as predictors for coronary artery calcium progression. A. Metabolic syndrome by WHO and its components. B. Metabolic syndrome by ATP-III and its components



* adjusted for age, sex, LDL-c, and smoking habit

PERSPECTIVAS FUTURAS

Como seguimento da linha de pesquisa em homeostase pressórica e complicações do Diabetes Melito tipo 2, pretendemos estudar o efeito de drogas bloqueadoras do sistema renina-angiotensina como medida de prevenção do desenvolvimento e progressão das complicações crônicas do Diabetes Melito tipo 2 através de técnicas de metaanálise.

OUTROS ESTUDOS REALIZADOS

Durante a realização do doutorado no Brasil e em San Diego foram obtidas outras publicações que estão listada abaixo:

1 - A prospective study of uric acid by glucose tolerance status and survival: The Rancho Bernardo. **Kramer CK**; von Muhlen, D; Jassal, S; Barrett-Connor, E. J Intern Med, *in press* (setembro/2009).

2 - A prospective study of abdominal obesity and coronary artery calcium progression in older adults. **Kramer CK**; von Muhlen D; Gross JL; Barrett-Connor, E. J Clin Endocrinol Metab, *in press* (setembro/2009)

3 - Hemoglobin A1c and diabetes diagnosis: The Rancho Bernardo Study. **Kramer CK**; Araneta, MR; Barrett-Connor, E. Diabetes Care, *in press* (setembro/2009)

4 - Treated hypothyroidism, cognitive function, and depressed mood in old age: The Rancho Bernardo Study. **Kramer CK**, von Muhlen D, Kritz-Silverstein D, Barrett-Connor E. Eur J Endocrinol. 2009 Sep 15. [Epub ahead of print]

5 - Risk factors for micro and macrovascular disease in black and white patients with type 2 diabetes mellitus. **Kramer CK**, Leitão CB, Pinto LC, Boza J, Silveiro SP, Gross JL, Canani LH. Rev Assoc Med Bras. 2009 May-Jun;55(3):308-14.

6 - Prevalence of diabetic retinopathy in patients with type 1 diabetes mellitus. Esteves JF, **Kramer CK**, Azevedo MJ, Stolz AP, Roggia MF, Larangeira A, Miozzo SA, Rosa C,

Lambert JH, Pecis M, Rodrigues TC, Canani LH. Rev Assoc Med Bras. 2009 May-Jun;55(3):268-73.

7 - Degree of catecholamine hypersecretion is the most important determinant of intra-operative hemodynamic outcomes in pheochromocytoma. **Kramer CK**, Leitão CB, Azevedo MJ, Canani LH, Maia AL, Czepielewski M, Paggi A, Rodrigues TC, Silveiro SP, Friedman R, Gross JL. J Endocrinol Invest. 2009 Mar;32(3):234-7.

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