



## **Influence of educational program directed at patients with prehypertension and hypertension on pressure values, biochemical variables, arterial stiffness and expression of metalloproteinases 2 and 9**

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### **ABSTRACT**

Considering that chronic disease treatment is seen as a challenge to health professionals, the adherence to therapy has been studied in several variables, such as socio-economic aspects, medicines, habits of daily life and food. The aim of the proposed study is to evaluate the influence of an educational program directed at patients with prehypertension and hypertension on pressure levels, biochemical variables, arterial stiffness and matrix metalloproteinase 9 (MMP-9). It is a case-control study. The participants will be allocated to three groups: 50 individuals with normal blood pressure; 80 with prehypertension; and 80 patients with hypertension in outpatient follow up with controlled blood pressure levels. Socio-demographic and behavioral data will be collected through interviews. Blood will be collected for biochemical analysis and the determination of MMP levels. Arterial stiffness will be evaluated through ambulatory blood pressure monitoring. The level of significance will be set to 5% ( $p < 0.05$ ).

### **Indexing terms/Keywords**

Hypertension; health promotion; adherence to treatment; arterial stiffness; extracellular matrix.

### **Academic Discipline And Sub-Disciplines**

Public Health; Health Education and Psychology; Hypertension pathophysiology.

### **SUBJECT CLASSIFICATION**

Chronic Vascular Disease Study: diagnosis and patient education effectiveness

### **TYPE (METHOD/APPROACH)**

Cross-sectional study; Survey/Interview

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## 1 INTRODUCTION

The high prevalence of arterial hypertension and its influence on cardiovascular disease and the mortality rate constitutes a serious public health problem that requires preventive strategies aimed as health promotion on the primary care level.<sup>1,2</sup> Broadening knowledge on individuals with chronic diseases and the identification of both internal and external difficulties related to such diseases favor the establishment of strategies aimed at increasing patient adherence to treatment. Indeed, non-adherence has serious negative impacts with regard to both health and associated costs, which are expected to reach as high as 65% of health expenditures worldwide by 2020.<sup>3,4</sup>

Cardiovascular disease is the leading cause of death worldwide. Hypertension is the most important factor in this process, as cardiovascular risk is directly proportional to BP levels.<sup>1,5</sup> The diagnosis of hypertension is based on systolic blood pressure (SBP) equal to or greater than 140 mmHg and diastolic blood pressure (DBP) equal to or greater than 90 mmHg in individuals who are not taking anti-hypertensive medication.<sup>6,7</sup>

The term prehypertension is used when SBP ranges from 120 to 139 mmHg or DBP ranges from 80 to 89 mmHg. This new classification was introduced due to the high mortality rates and high conversion rates to clinical hypertension among individuals with a marginal increase in BP.<sup>8</sup>

Vascular remodeling and arterial stiffness are among the different physiopathogenic mechanisms that characterize the multifactor etiology of arterial hypertension.<sup>9</sup> Arterial stiffness can be evaluated through noninvasive techniques, such as pulse wave velocity,<sup>10,11</sup> and central BP, that also furnishes information on arterial stiffness through the analysis of the augmentation index (AI). This variable is strongly correlated with age and sex and is considered an important marker of cardiovascular risk and the development of lesions in target organs when above the desired limit for age.<sup>12,13</sup>

Moreover, there has been growing interest in the study of proteolytic enzymes known as matrix metalloproteinases (MMPs), the levels of which are increased in patients with a poor cardiovascular outcome.<sup>14</sup> The increased activity of these enzymes can impair vascular relaxation and consequently contribute to hypertrophy of arterial walls, leading to vascular dysfunction and an increase in arterial stiffness.<sup>15,16</sup> Despite the reports of this association, few studies have addressed MMP levels as markers of arterial stiffness in populations with different degrees of blood pressure (BP).

The proposed study will involve patients with prehypertension and hypertension and will have the following aims: identify difficulties and reasons that lead to adherence or non-adherence to treatment; determine knowledge on the part of such individuals regarding the risks of non-adherence; evaluate similarities and differences in the behavior of such individuals after undergoing an educational program; clarify the physiopathogenic mechanisms of prehypertension and hypertension through an analysis of arterial stiffness as a marker of cardiovascular risk and correlate the findings with MMPs in individuals with normal BP, prehypertension and hypertension; and contribute toward improving the quality of care offered by health professionals.

## 2 METHODS/DESIGN

### 2.1 Study population

Following approval from the local ethics committee, 210 individuals between 30 and 70 years of age will be selected to participate in the study. The participants will be allocated to one of three groups matched for age and gender: Group 1 (G1) – 50 individuals with normal BP (<120/80 mmHg); Group 2 (G2) – 80 individuals with prehypertension (BP: 120-139/80-89 mmHg); and Group 3 (G3) – 80 patients with controlled hypertension (< 140/90 mmHg) in outpatient follow up. The sample size was estimated to detect differences among the three groups. The following will be the exclusion criteria: current pregnancy; low life expectancy; previous diagnosis of arterial hypertension or previous use of anti-hypertensive medication (valid for G1 and G2); chronic disease that limits participation in the study (e.g., cancer); cognitive impairment that limits participation in the study; impossibility of measuring BP; and refusal to sign a statement of informed consent (previously approved by the ethics committee).

### 2.2 Definition of prehypertension and hypertension

All participants will be submitted to an evaluation of BP. Three measures will be taken during two visits using a validated sphygmomanometer (OMRON M7 model, Omron Health Care, Kyoto, Japan) following the recommendations of the Brazilian Hypertension Guidelines.<sup>9</sup> The mean of the last two measures of each visit obtained from the arm with the highest BP value will be used for the definition of prehypertension. Prehypertension will be defined when SBP is between 120 and 139 mmHg or when DBP is between 80 and 89 mmHg. Hypertension will be defined when BP is equal to or greater than 140/90 mmHg or when the individual uses anti-hypertensive medication.

All participants will be submitted to ABPM on a standardized day with a cuff appropriate to the size of the individual's arm. SBP and DBP will be determined from 24-hour ABPM and mean values obtained in the 24-hour period, during waking hours and during sleeping hours will be considered in the analysis. Pulse pressure (PP) will be calculated from mean SBP and DBP during the periods analyzed (24 hours, waking hours and sleeping hours), as follows  $PP = SBP - DBP$ . Nocturnal dipping will be standardized as a  $\geq 10\%$  drop in SBP from waking to sleeping hours. The SpaceLabs 90207 system (Spacelabs Healthcare, Issaquah, Washington, USA) will be used for ABPM, which has been validated based on the protocol of the British Hypertension Society and Brazilian Hypertension Guidelines.<sup>17,18</sup>



## 2.3 Evaluation of biochemical parameters

An investigative protocol will be used to gather information on patient history, associated diseases, medications in use, previous illnesses and family history. Weight and height will be determined using an anthropometric scale. Peripheral blood will be collected for biochemical analysis (glycemia, creatinine and lipid profile). The lipid profile will be evaluated through the determination of total cholesterol, LDL, HDL and triglycerides after 12 hours of fasting. The glomerular filtration rate will be estimated using the formula proposed by the Modification of Diet in Renal Disease study.<sup>20</sup> This calculation will be performed using a specific software program and will take into account plasma creatinine level, age, ethnicity and gender.<sup>21</sup>

## 2.4 Arterial stiffness

Data on arterial stiffness will be acquired using the Mobil-O-Graph NG<sup>®</sup> equipment, 24-hour ABPM and pulse wave analysis. The data furnished by the Mobil-O-Graph NG<sup>®</sup> equipment include pulse wave velocity, AI, reflection coefficient, central arterial pressure and peripheral vascular resistance.

## 2.5 Metalloproteinase levels

Serum concentrations of MMP-2 and MMP-9 will be determined through enzyme-link immunosorbent assays (ELISA, R&D Systems, Inc., Minneapolis, MN, USA). The samples will be separated by centrifugation of the plasma and stored at -80°C until analysis. The sensitivity of the test will be 0.2 ng/ml for MMP-9 and 0.16 ng/ml for MMP-2. Individual variability will not exceed 10%. The pro-enzyme and active form of the collagenases will be recognized by monoclonal antibodies directed at MMP-2 and MMP-9.<sup>22,23</sup>

## 2.6 Analysis of behavioral profile

A semi-structured interview will be administered to all participants for the identification of personal data (age, gender, socioeconomic and demographic characteristics). The groups with prehypertension and hypertension will also be asked about living habits, time elapsed since diagnosis, presence of associated diseases, knowledge and perceptions regarding the disease, the importance of treatment and factors that either facilitate or hamper adherence to treatment.

# 3 RESULTS

## 3.1 Statistical analysis

Descriptive analysis will be performed of the quantitative variables, with the presentation of mean and standard deviation values. The t-test will be applied for quantitative variables and the chi-square test and test of proportions will be used for qualitative variables. All analyses will be performed using the Minitab program, version 15.0, with the level of significance set to 5% ( $p < 0.05$ ).

# 4 DISCUSSION

The treatment of chronic disease is seen as a challenge to health professionals because of the need to care continuously. Thus, adherence to therapy, defined as the joint activity in which the patients understands, agrees and follows the prescription established, has been studied in several variables, such as socio-economic aspects, number of drugs, pills and number of daily doses, effects side, treating interference in the activities and habits of daily life and food, the attitude and behavior of the patient in relation to their health status and the interaction and communication between patient and health professional<sup>23-25</sup>.

In this context, hypertension, a chronic syndrome of asymptomatic evolution, is one of the clinical situations in which adherence was evaluated by attending medical appointments, by following the prescribed medications and changes in lifestyle, becomes crucial in the final outcome treatment, which is the control of blood pressure, reduction of hypertensive complications and cardiovascular disease, and better quality of life<sup>23,26,27</sup>.

Studies show that even in countries where knowledge of hypertension is high as in the United States, where 75 % of hypertensive patients are aware of their situation, only about 50 % use of medication, and only 27.5 % had effective control of blood pressure<sup>27</sup>. And, despite the greater control and adherence to treatment of hypertension observed in the past 30 years, cardiovascular disease remains the leading cause of death worldwide, justifying the need for improvement and expansion of educational programs<sup>27,28</sup>.

Associated therapy has a fundamental importance for early diagnosis of hypertension. In this context, studies have been devoted to elucidation of the role played by metalloproteinase<sup>5</sup> (MMP -9), gelatinase responsible for the degradation of collagen types I, IV, V, VI, X and XI, as well as elastin, and fibronectin<sup>29,30</sup> and associated with the occurrence of atherosclerosis, myocardial infarction and diabetes mellitus type 2<sup>16,22,31-33</sup>.

In an experimental study Flamant et al (2007) showed that induced by administration of angiotensin II hypertension was accompanied by increased expression of MMP -9, as well as the reduction of its activity was associated with increased arterial stiffness and pulse pressure<sup>34</sup>. Thus, activation of MMP -9 was identified as beneficial in the early development of hypertension by acting degradation result in vascular diameter and compliance, relieving the elevation of blood pressure. However, latterly, maintaining the activity of MMP -9 has been held responsible for increased migration and cellular hypertrophy, with consequent pathological vascular remodeling and arterial medial thickening layer. Similarly, other studies



showed an imbalance between activating and inhibiting metalloproteinase degradation of elastin and calcification resulting in arterial hypertension<sup>35, 36</sup>. Chen et al (2011) suggested that even though the pathophysiology of vascular calcification form a complex, the inhibition of MMP-9 might prevent its development<sup>27</sup>. Whereas the increase in MMP -9 impairs endothelium-dependent relaxation resulting in vascular and vascular thickening, its inhibition has been valued in many studies to represent a therapeutic strategy in the treatment of hypertension and prevention of its consequences<sup>37</sup>. Despite recent findings suggest the circulating MMP -9 as a key factor for early diagnosis and treatment of hypertension, its physiological and pathological role remains under investigation because of divergence of results obtained in clinical studies, whose cause has been attributed to differences in study groups, including the severity of hypertension, presence of comorbidities, and medication therapy adopted<sup>38</sup>. Thus, well-designed and controlled clinical studies are of vital importance to elucidate the prognostic value of MMP -9 and the therapeutic effect of its inhibition.

## Research status

This study is currently recruiting patients with prehypertension and hypertension and collecting baseline and follow-up data. Recruitment is expected to end in September 2014.

## Competing interests

The authors declare no competing interests.

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