Correlation between Metabolic Syndrome and Its Components with Pulse Pressure in Persons without Apparent Disease

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SUMMARY

Background

Pulse pressure depends mostly on arterial wall stiffness. Several studies have focused on the fact that many factors, including the metabolic syndrome or its components, interact to impact on great vessels elastic properties, increasing arterial wall stiffness.

Objective

To evaluate the influence of the metabolic syndrome and its components on pulse pressure in persons without any apparent disease.

Material and Methods

A total of 1.155 subjects without demonstrable disease were randomly selected. The metabolic variables defining metabolic syndrome (ATP III) were recorded: fasting HDL-cholesterol ≤ 40/50 mg/dl (men/women), fasting triglycerides ≥150 mg/dl, fasting glycemia ≥100 mg/dl, waist circumference ≥102/88 cm (men/women) and systolic/diastolic blood pressure ≥130/85 mm Hg. Patients' pulse pressure values were compared among different groups according to gender and age. The frequency of the metabolic syndrome components was determined and pulse pressure was adjusted by gender, age and all the components using multiple linear regression analysis. The adjusted value of pulse pressure corresponding to each metabolic syndrome component was determined and compared to that of normal subjects. Finally, adjusted pulse pressure was calculated according to the possible combinations of three factors or greater (diagnostic criteria of metabolic syndrome) and was compared with that of individuals without any component of the metabolic syndrome.

Results

General characteristics of the 1.155 individuals: men 62%, age 38±9 years (range 20-66), waist circumference 89±13 cm, triglycerides 107±74 mg/dl, glycemia 82±16 mg/dl, HDL-cholesterol 48±13 mg/dl, systolic blood pressure 124±14 mm Hg, diastolic blood pressure 78±9 mm Hg, pulse pressure 46±9 mm Hg.
Age: 38±9 years in men (n=712) and 37±9 years in women (n=443); p=ns. Pulse pressure was 48±8 mm Hg in men versus 43±9 mm Hg in women; p<0.001. Influence of age on pulse pressure: 45±8 in individuals <35 years versus 47±9 in ≥35 years; p<0.001. Frequency of metabolic syndrome components: waist circumference ≥102/88 cm: 18%, glycemia ≥100 mg/dl: 7%, triglycerides ≥150 mg/dl: 17%, HDL-cholesterol ≤40/50 mg/dl: 45%, systolic blood pressure ≥130 mm Hg: 40%, diastolic blood pressure ≥85 mm Hg: 16%. When pulse pressure adjusted by each component of the metabolic syndrome was compared to that of controls, the following values were obtained: waist circumference ≥102/88 cm: 48±4 versus 46±3, glycemia ≥100 mg/dl: 52±5 versus 46±3, triglycerides ≥150 mg/dl: 48±3 versus 46±4, HDL-cholesterol ≤40/50 mg/dl: 44±3 versus 47±3; systolic blood pressure ≥130 mm Hg: 48±4 versus 45±3; diastolic blood pressure [3]85 mm Hg: 48±5 versus 46±3, all p<0.001.
Finally, adjusted pulse pressure according to the possible combinations of three factors or greater was calculated and compared with that of individuals without any component of the metabolic syndrome: 49±5 versus 46±3, p<0,001.

Conclusions

The metabolic syndrome and/or its components induce pulse pressure elevation, except for HDL-cholesterol. This effect seems to be independent of age, gender and the eventual interaction of the variables analyzed.

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Palabras clave > Metabolic Syndrome - Pressure - Arterial Pulse - Hypertension - Risk Factors

Abreviaturas >

ATP III	Adult Treatment Panel III	hs-CRP	High sensitivity C-reactive protein
HDL-C	High density lipoprotein-cholesterol	PP	Pulse pressure
GL	Glycemia	adj-PP	Adjusted pulse pressure
DBP	Diastolic blood pressure	MS	Metabolic syndrome
SBP	Systolic blood pressure	TG	Triglycerides
WC	Waist circumference		

BACKGROUND

Routine blood pressure evaluation considers measuring systolic and diastolic blood pressure; in consequence, the studies that confirmed the importance of blood pressure as a cardiovascular risk factor have focused on these values, which are the expression of blood pressure changes within the arteries during the cardiac cycle. However, the principal components of blood pressure consist of both a steady component (mean arterial pressure) and a pulsatile component (pulse pressure). Mean arterial pressure (MAP) is especially related to peripheral resistance, while pulse pressure (PP) is linked to arterial stiffness and to the reflected wave. In addition, they both depend on cardiac output. (1, 2)

The role of each of these components to predict cardiovascular risk is still under discussion. Data from the Framingham Heart Study suggest that PP is better than systolic or diastolic blood pressure in predicting risk for coronary heart disease in subjects older than 50 years, while the opposite occurs in younger persons. (1-4)

Increased large-artery stiffness is a physiological response to aging and an independent cardiovascular risk factor. Several conditions as hypertension, diabetes and kidney failure, are associated with increased arterial stiffness. (4-9) Different studies have demonstrated increased arterial stiffness in subjects with metabolic syndrome or with some of its components. (10-15) The evidence also indicates that the age-related increase in arterial stiffness is greater among people with MS. (16, 17) Obesity has also been associated with increased arterial stiffness in apparently healthy adolescents and young adults. (18-20) On the other hand, resolution of metabolic syndrome may be associated with attenuation of the progression of arterial damage. (21)

All these data suggest that MS affects the elastic properties of arterial walls, increasing arterial stiffness. This may explain increased cardiovascular risk in subjects with MS.

The effect of metabolic syndrome on arterial stiffness is expressed by abnormalities in PP. (22) The goal of the present study was to determine the correlation between MS and its components with elevated PP in persons without apparent disease.

MATERIAL AND METHODS

We conducted a descriptive and cross-sectional study on a randomly selected population of patients referred from primary care physicians for a routine medical examination. Data were collected in three centers from January 2006 to December 2008. The investigators collaborating in this study received instructions about how to collect and enter patients' information into the medical record. All patients who sought medical care for a routine examination and accepted to participate in the study were consecutively included.

Inclusion criteria: outpatients of both genders > 18 years old who were apparently healthy and actively working.

Exclusion criteria: hypertension or any other heart disease; concomitant conditions or treatment with any drug that might affect the patient registry data.

Measurements

Blood pressure measurement: blood pressure was measured with the patient in the sitting position, using a recently calibrated aneroid sphygmomanometer with a cuff with an appropriate bladder size matched to the size of the arm. Two determinations were made at a 5-minute interval and the average value was recorded.

Anthropometric measurements: waist circumference (WC) was determined using a non-stretchable measuring tape with the patient in the standing position at the end of expiration. Waist circumference was determined twice at the midpoint between the lower rib margin and the iliac crest, and the average of both observations was recorded.

Blood samples were obtained after a 12-hour fast for measuring high density lipoprotein-cholesterol (HDL-C), triglycerides (TG) and glycemia (GL), and were analyzed in the same day with an autoanalyzer using the corresponding reagents.

The MS variables defined by the ATP III according to gender (23, 24) were recorded: WC (cm) ≥ 102/88 and (in mg/dl and in fasting condition) HDL-C ≤ 40/50, TG ≥ 150, and GL ≥ 100; systolic blood pressure (mm Hg) ≥ 130 and/or diastolic blood pressure ≥ 85 (SBP/DBP). Pulse pressure (mm Hg) was calculated as the difference between SBP and DBP.

Firstly, patients' PP values were compared among different groups according to gender and age. Then, the frequency of the MS components was determined and PP was adjusted by gender, age and all the components using logistic regression analysis. Systolic and diastolic blood pressure values were colinear with PP (calculated as the difference between both values) and were excluded from the model. The adjusted value of PP corresponding to each component of the metabolic syndrome was then determined and compared to that of normal subjects. Finally, adjusted PP was calculated according to the possible combinations of three factors or greater (diagnostic criteria of metabolic

syndrome) and was compared with that of subjects without any component of the MS.

Statistical Analysis

Data were analyzed using SPSS 7 software package. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as percentage. The results were compared using the Student's t test and/or Mann-Whitney rank-sum test. Multiple linear regression models were used to adjust for age, gender and the other variables. A two-tailed p value < 0.05 was considered statistically significant.

RESULTS

General characteristics of the 1155 participants: men 62%, age 38 ± 9 years (range 20-66), WC 89 ± 13 cm, TG 107 ± 74 mg/dl, GL 82 ± 16 mg/dl, HDL-C 48 ± 13 mg/dl, SBP 124 ± 14 mm Hg, DBP 78 ± 9 mm Hg, PP 46 ± 9 mm Hg.

Age: 38 ± 9 years in men (n = 712) and 37 ± 9 years in women (n = 443); p = ns. Pulse pressure was 48 ± 8 mm Hg in men versus 43 ± 9 mm Hg in women; p < 0.001. In addition, PP tended to be higher from the third decade. In patients < 35 years, PP was significantly lower compared to those ≥ 35 years: s: 45 ± 8 versus 47 ± 9 mm Hg; p < 0.001 (Table 1).

The frequency of the different components of the MS is described in Table 2.

As we knew that the degree of interaction among the variables was high, pulse pressure was adjusted by gender, age and all the components of the MS, excluding SBP and DBP, to control for confounding variables.

When PP adjusted by each component of the metabolic syndrome was compared to that of controls, we noted a significant increase in PP in the presence of any of them, except for HDL-C < 40/50 (Table 3).

Finally, adjusted PP was calculated according to the possible combinations of three factors or greater of the MS and was compared with that of subjects without any component of the MS 49 ± 5 versus 46 ± 3 mm Hg; p < 0.001 (Figure 1). The characteristics of both groups are described in Table 4.

DISCUSSION

Undoubtedly, systolic blood pressure continuously increases with age, while diastolic blood pressure increases until the age of 50-60 years and then tends to decrease. (3, 5) In consequence, PP exhibits a slow increase until the age of 60 and then increases rapidly. These changes in systolic blood pressure and PP can be explained by the progression in wall stiffness of the large arteries that occurs with aging. The elastin in the arterial walls is replaced by collagen, producing hypertrophy and fibrosis of the muscular layer This process is invariable related to aging and may be accelerated by different factors, particularly by hypertension. (1, 7) Both systolic blood pressure and PP are directly related to atherosclerosis and promote vascular damage, constituting important markers of the latter. (2, 4)

Similarly to other studies, we found a direct correlation between PP and age. However, the cut-off value of PP to establish significant differences was 35 years,

Table 1. Pulse pressure according to gender and age

	Hombres (712)	Mujeres (443)	< 35 años (511)	≥ 35 años (644)
PP	48 ± 8	43 ± 9	45 ± 8	47 ± 9
p <	0.001		0.001	

Table 2. Frequency of the different components of the metabolic syndrome

Factor	PC ≥ 102/88	TG ≥ 150	GL ≥ 100	C-HDL ≤ 40/50	PAS ≥ 130	PAD ≥ 85
Frecuencia	18%	17%	7%	45%	40%	16%

WC: Waist circumference TG: Triglycerides. GL: Glycemia HDL-C: High density lipoprotein-cholesterol. SBP: Systolic blood pressure. DBP: Diastolic blood pressure.

Table 3. Pulse pressure adjusted according to each component of the metabolic syndrome versus controls

Factor	WC		TG		GL		HDL-C		SBP		DBP	
	≥102/88	< 102/88	≥150	< 150	≥100	< 100	≤40/50	> 40/50	≥130	< 130	≥ 85	< 85
PPaj	48 ± 4	46 ± 3	48 ± 3	46 ± 4	52 ± 5	46 ± 3	44 ± 3	47 ± 3	48 ± 4	45 ± 3	48 ± 5	46 ± 3
p <	0.001		0.001		0.001		0.001		0.001		0.001	

WC: Waist circumference TG: Triglycerides. GL: Glycemia HDL-C: High density lipoprotein-cholesterol. SBP: Systolic blood pressure. DBP: Diastolic blood pressure. ad-PPaj: Adjusted pulse pressure.

an age too much lower than expected according to we have previously mentioned. This result may be due to the fact of including a relatively young population as a reference.

We also found that PP was greater in men compared to women of the same age. However, the relation between PP and gender is controversial. Some studies have reported that PP is greater among women, yet most reports show dissimilar results. (4, 6)

Different studies have demonstrated increased arterial stiffness in subjects with metabolic syndrome or with some of its components, even in the absence of diabetes. (10-17) In this sense, our study demonstrates that, in apparently healthy people, PP is associated with the components of the MS, suggesting that the interaction of these components is unfavorable to arterial wall elasticity.

The detrimental effect of the MS or its components on arterial wall elasticity may be due to the release of proinflammatory cytokines or leptin from the visceral fat. Abnormalities in vascular relaxation (probably due to less availability of endothelium-derived nitric oxide which is connected with insulin resistance) and reduction in adiponectin synthesis may also explain this effect. (25-28)

Metabolic syndrome is associated with increased sympathetic activity, endothelial dysfunction and insulin resistance which may act in concert, increasing arterial stiffness and pulse pressure. (27-30)

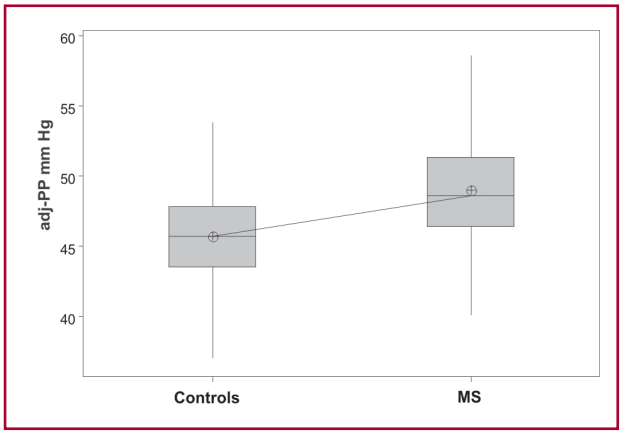

Fig. 1. Adjusted pulse pressure, metabolic syndrome versus controls. adj-PP: adjusted pulse pressure. MS: Metabolic syndrome.

Inflammation is another determinant factor and is represented by increased high sensitivity C-reactive protein (hs-CRP) and higher pulse wave velocity: the reflected wave returns earlier into the forward wave of the pulse waveform. (31) Inflammation plays a key role in the development of complications related to MS; in addition, it is well-known that hs-CRP has a significant correlation with insulin resistance and with each component of the MS. (32) In consequence, an increasing degree of vascular inflammation may be important in increasing arterial stiffness and PP in patients with MS. In addition, increased oxidative stress and glycosylation of macroproteins may alter the structure of collagen and elastin, diminishing arterial elasticity. (33)

Visceral fat accumulation is associated with insulin resistance, hyperglycemia and diabetes. (27) There is evidence regarding the presence of increased aortic stiffness in patients with diabetes or with abnormalities in glucose metabolism. (34, 35) Hyperglycemia may stimulate collagen synthesis and induce glycosylation of matrix proteins, modifying the structure of the elastic fibers of the arterial wall. (33) Hyperinsulinemia increases the sympathetic tone, resulting in increased heart rate and blood pressure and creating an additional mechanical burden against the vascular system. (36) Elevated PP induces greater wall stress and increases fracture and fatigue of the elastic components of the arterial wall. In this way, the intima is more prone to damage, increasing the risk of atherosclerosis and thrombosis. (2)

Elevated PP increases left ventricular workload, end-systolic pressure and myocardial oxygen uptake, which in turn promote cardiac hypertrophy. (2) Increased myocardial oxygen consumption together with a reduction in diastolic blood pressure may compromise coronary perfusion, leading to myocardial ischemia. (1, 2) The combination of both effects reduces arterial elasticity and increase PP, a marker of adverse cardiovascular events. (1-5)

Our results indicate that PP is greater in subjects with MS compared to controls. At the same time, PP increased significantly in subjects with a MS component. However, we noted that PP had a direct relation with HDL-C levels after adjusting for the variables related. A relation exists between HDL-C and hereditary and environmental factors such as physical activity, smoking habits and alcohol intake. (23) In the present study, the distribution of HDL-C levels

Table 4. Characteristics off subjects with MS and without MS

SM	N	H	Edad	PC	TG	GL	C-HDL	PAS	PAD
No	307	56%	34 ± 9	84 ± 11	74 ± 26	77 ± 8	57 ± 11	115 ±11	72 ± 9
Yes	121	77%	44 ±9	106 ±13	177±117	98 ± 30	40 ± 8	139 ± 11	88 ± 8

MS: Metabolic syndrome. N: Number. M: Men. WC: Waist circumference. TG: Triglycerides. GL: Glycemia. HDL-C: High density lipoprotein-cholesterol. SBP: Systolic blood pressure. DBP: Diastolic blood pressure.

may be influenced by residual confounding variables that have not been previously evaluated.

These data seem to support the concept that MS could reduce arterial wall elasticity or accelerate vascular aging. The latter includes several changes in the arterial wall, increasing stiffness and pulse pressure. (18)

Study limitations

Our study evaluating the role of MS and its components in elevating PP has some limitations. Firstly, our conclusions are based on data obtained from a cohort of relatively young and healthy subjects without cardiovascular disease in whom we did not evaluate dietary habits or socioeconomic status. As the components of MS and PP increase with age, the results may be different in elder subjects. Secondly, as this is a cross-sectional study, we could not evaluate if PP is a marker of cardiovascular events. Thirdly, subjects with hypertension or under antihypertensive therapy were excluded from the study. In consequence, our results may be interpreted in different ways. The characteristics of the study population indicate that these results may not be extrapolated to patients under antihypertensive treatment or to the general population. Fourthly, peripheral PP is greater than central PP (amplification) in young people and this difference gradually decreases with aging. Therefore, PP measured in the brachial artery might no reflect accurately the value of central PP, which is a better risk marker. Fifthly, the importance of each component of MS as a predictor of elevated PP may not be applied individually; the accuracy and precision might be improved by calculating the average blood pressure measured in several medical visits or using ambulatory blood pressure monitoring. Finally, PP is a surrogate marker of arterial stiffness; the use of direct indicators, as pulse wave velocity or aortic augmentation index, may be more accurate.

However, despite these potential limitations, our study may be useful to identify subjects at greater risk who might benefit from a more aggressive control of the risk factor defining the metabolic syndrome.

CONCLUSIONS

The metabolic syndrome and/or its components induce pulse pressure elevation, except for HDL-cholesterol. This effect seems to be independent of age, gender and the eventual interaction among the variables analyzed. In these subjects, elevated pulse pressure might reflect increased stiffness in the large arteries and therefore might contribute to explain the greatest cardiovascular risk associated with the metabolic syndrome.

RESUMEN

Relación del síndrome metabólico y sus componentes con la presión del pulso en personas sin enfermedad aparente

Introducción

La presión del pulso depende en gran medida de la rigidez arterial. Varios estudios se han centrado en el hecho de que diversos factores, entre ellos el síndrome metabólico o suscomponentes, intermedian cambios que afectan en forma adversa las propiedades elásticas de las grandes arterias, acentuando su rigidez.

Objetivo

El propósito de este trabajo de investigación fue evaluar la influencia del síndrome metabólico y sus componentes sobre la presión del pulso en personas sin enfermedad aparente.

Material y métodos

Se seleccionaron al azar 1.155 individuos sin enfermedad demostrable. Se registraron las variables que definen el síndrome metabólico (ATP III): en mg/dl y en ayunas, colesterol HDL ≤ 40/50 (hombres/mujeres), triglicéridos ≥ 150, glucemia ≥ 100, perímetro de la cintura (cm) ≥ 102/88 (hombres/mujeres) y presión arterial sistólica/diastólica ≥ 130/85 mm Hg. Se compararon los valores de la presión del pulso obtenidos al agrupar a los participantes por sexo y edad. Se estableció la frecuencia de los factores que definen el síndrome metabólico y mediante regresión lineal se ajustó la presión del pulso por sexo, edad y por el conjunto de ellos. A continuación se determinó el valor ajustado de la presión del pulso correspondiente a cada factor del síndrome metabólico y se comparó con el de sujetos normales. Finalmente, se calculó la presión del pulso ajustada de acuerdo con las posibles combinaciones de tres o más factores (criterio diagnóstico de síndrome metabólico) y se comparó con la de individuos en los que no se hallaba presente ningún componente del síndrome.

Resultados

Características generales de los 1.155 individuos: hombres 62%, edad 38 ± 9 años (rango 20-66), perímetro de la cintura 89 ± 13 cm, triglicéridos 107 ± 74 mg/dl, glucemia 82 ± 16 mg/dl, colesterol HDL 48 ± 13 mg/dl, presión arterial sistólica 124 ± 14 mm Hg, diastólica 78 ± 9 mm Hg, presión del pulso 46 ± 9 mm Hg.

Edad: 38 ± 9 años los hombres (n = 712) y 37 ± 9 años las mujeres (n = 443); p = ns. La

presión del pulso fue de 48 ± 8 mm Hg en los hombres versus 43 ± 9 mm Hg en las mujeres; p < 0,001. Efecto de la edad sobre la presión del pulso: 45 ± 8 en individuos < 35 años versus 47 ± 9 en ≥ 35 años; p <0,001. Frecuencia de los distintos elementos que definen el síndrome metabólico: perímetro de la cintura ≥ 102/88 cm: 18%, glucemia ≥ 100 mg/dl: 7%, triglicéridos ≥ 150 mg/dl: 17%, colesterol HDL ≤ 40/50 mg/dl: 45%, presión arterial sistólica ≥ 130 mm Hg: 40%, diastólica ≥ 85 mm Hg: 16%. Al comparar la presión del pulso ajustada delimitada por cada factor del síndrome metabólico con la de los controles se obtuvo: perímetro de la cintura ≥ 102/88 cm: 48 ± 4 versus 46 ± 3, glucemia ≥ 100 mg/dl: 52 ± 5 versus 46 ± 3, triglicéridos ≥ 150 mg/dl: 48 ± 3 versus 46 ± 4, colesterol HDL ≤ 40/50 mg/dl: 44 ± 3 versus 47 ± 3; presión arterial sistólica ≥ 130 mm Hg: 48

± 4 versus 45 ± 3; diastólica ≥ 85 mm Hg: 48 ± 5 versus 46 ± 3, todas p < 0,001. Por último, se comprobó la presión del pulso ajustada de acuerdo con las posibles combinaciones de tres o más factores y se comparó con la de individuos en los que no se hallaba presente ningún componente del síndrome metabólico; el resultado fue 49 ± 5 versus 46 ± 3, p < 0,001.

Conclusiones

El síndrome metabólico y/o sus componentes individuales inducen una elevación de la presión del pulso, a excepción del colesterol HDL. Este efecto parece ser independiente de la edad, del sexo y de la eventual interacción entre las variables analizadas.

Palabras claves> Síndrome metabólico - Presión - Pulso arterial - Hipertensión - Factores de riesgo

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Disclosure
None declared.