Available online at www.sciencedirect.com
ScienceDirect
Diabetes & Metabolism 33 (2007) 183–188
Diabetes & Metabolism
http://france.elsevier.com/direct/diabet

Original article

Ageing and blood pressure modulate the relationship between metabolic syndrome and aortic stiffness in never-treated essential hypertensive patients. A comparative study

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Received 15 September 2006; accepted 12 November 2006
Available online 28 February 2007

Abstract

Objective. – The aim of this study was to evaluate the impact of the metabolic syndrome (MS) and its components as defined by the National Cholesterol Education Program Adult Treatment Panel III on arterial stiffness in untreated hypertensive patients.

Methods. – This was a cross sectional multi-center study performed in 46 healthcare centers, from 14 countries involved in the Complior study. Four hundred and forty patients (55% male) aged 18–73 years, with untreated essential hypertension were selected at inclusion. All patients underwent a full evaluation for all the risk factors representing the MS and an assessment of arterial stiffness using automatic measurement of carotid-femoral pulse wave velocity (PWV).

Results. – In the overall population significant correlations were found, respectively, between PWV, MS ($R = 0.2$, $P < 0.001$) and gender ($R = 0.11$, $P = 0.023$) where PWV was higher in women. After adjustment for age and systolic blood pressure (SBP), analysis of covariance showed an independent effect of the MS on PWV, this effect increased with ageing and SBP especially after 47 years (age median, $P = 0.0047$). Moreover, increase of mean PWV was highly associated with the number of MS factors in global population ($P < 0.001$). These findings suggest that MS leads to early arterial wall ageing.

Conclusions. – Presence of MS induces an increase of arterial stiffness in untreated hypertensive patients independently from age and SBP. The increase of PWV is proportional to number of risk factors and affects principally patients after mid-age of 47 years where MS has ageing effects on arterial stiffness.

Résumé

Le vieillissement et la pression artérielle modulent la relation entre le syndrome métabolique et la rigidité aortique chez l'hypertendu essentiel jamais traité. Une étude comparative.

Objectif. – Le but de cette étude était d'évaluer l'effet du syndrome métabolique (SM) et de ses composants comme il a été défini par la NCEP-ATPIII « National Cholesterol Education Program Adult Treatment Panel III » sur la rigidité artérielle chez l'hypertendu jamais traité.

Méthodes. – Cette étude transversale multicentrique a été réalisée dans 46 centres (14 pays) faisant partie de l'étude COMPLIOR. 440 hypertendus non traités (55 % d'hommes), âgés entre 18 et 73 ans ont été sélectionnés à l'inclusion. Une évaluation des facteurs de risque représentant le syndrome métabolique ainsi qu'une évaluation de rigidité artérielle se basant sur la mesure automatique de la vitesse carotidofémorale de l'onde de pouls (VOP) ont été effectuées chez les patients hypertendus.

Résultats. – Dans la population globale, l'analyse univariée montrait des corrélations significatives entre la VOP, le SM ($r = 0.2$, $P < 0{,}001$) et le sexe ($r = 0{,}11$, $p = 0{,}023$) où la VOP était plus élevée dans le groupe des femmes. Après l'ajustement pour l'âge et la pression artérielle systolique (PAS), l'analyse de covariance a montré un effet indépendant du SM sur la VOP, cet effet augmentait avec l'âge et la PAS particulièrement après 47 ans (médiane d'âge, $P = 0{,}0047$). De plus, l'augmentation de la VOP était fortement associée au nombre des facteurs du SM dans la population globale ($P < 0{,}001$). Ces résultats suggèrent que le SM favorise le vieillissement de la paroi artérielle.

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doi:10.1016/j.diabet.2006.11.011

Conclusion. – La présence du syndrome métabolique induit une augmentation de la rigidité artérielle chez les hypertendus non traités indépendamment de l'âge et de la PAS. L'augmentation de la VOP est proportionnelle au nombre de facteurs de risque et affecte principalement des patients âgés de plus de 47 ans pour lesquels le SM, facteur de vieillissement artériel, amplifie la rigidité artérielle.

Keywords: Arterial stiffness; Hypertension; Metabolic syndrome; Pulse wave velocity; Syndrome X

Mots clés : Rigidité artérielle ; Hypertension ; Syndrome métabolique ; Vitesse de l'onde de pouls ; Syndrome X

1. Introduction

Structural and functional properties of the arterial wall have been described to be altered at early stages of hypertension [1]. It is well recognized that ageing and high blood pressure (BP) lead to stiffer arteries and therefore increase morbidity and mortality. Moreover, other risk factors with complex metabolic disorders, like obesity, insulin resistance, and dyslipidemia, contribute to arterial stiffness increase [2–4]. In 1988, Dr. G. Reaven [5] defined a new syndrome called syndrome X or metabolic syndrome (MS) as the cluster of more than two risk factors for cardiovascular disease (CVD) that includes combination between hypertension, hypertriglyceridemia, low-levels of high-density lipoprotein, insulin resistance, and/or obesity. Different diagnosis criteria for this syndrome have been suggested by the World Health Organization (WHO) [6], the American Heart Association (AHA) [7], and the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) [8] which consists in having three components or more from the risk factors cluster. The definition of the WHO chose type 2 diabetes mellitus (based on the insulin resistance level) as a principle component for the MS diagnosis; whereas the NCEP and the AHA gave the choice between the five components knowing that they predict not only diabetes, but also cardiovascular mortality in lower-risk subjects [9].

Several studies have shown that the MS is increasingly recognized as a strong predictor of patient risk for developing CVD and target organ damage (TOD) [10–13]. In untreated essential hypertensive, Cuspidi et al. [14] reported a high prevalence of MS and a high relationship between MS and left ventricular hypertrophy (LVH), but not with carotid intima-media thickness (IMT). In community-dwelling volunteers, with and without high BP (Baltimore Longitudinal Study on Ageing), Scuteri et al. [15] showed a strong independent association between MS and increased thickness and stiffness (B-mode ultrasonography) of the carotid artery. More recently, Schillaci et al. [16] and Mule et al. [17] confirmed this association in an untreated hypertensive population. These findings lead us to make the assumption of an independent relation between MS and arterial stiffness as evaluated by PWV. The aim of this study was to assess the association between PWV and the different parameters of MS in never-treated age-stratified hypertensive patients.

2. Methods

Patients inclusion was performed from the international cross sectional multi-center Complior study. Study design and inclusion criteria were published in details elsewhere [18].

2.1. Patients

Male and female patients were included by 46 health care centers (14 countries) in this study provided they were aged 18–73 years, and presented an untreated essential hypertension defined as a diastolic blood pressure (DBP) ≥ 95 and ≤ 114 mmHg, and/or a systolic blood pressure (SBP) ≥ 160 and ≤ 200 mmHg. Main exclusion criteria were: secondary hypertension, complicated hypertension with recent CVDs (<6 months), arterial stenosis > 70%, and obesity defined as a body mass index (BMI) ≥ 35 kg/m^2.

2.2. Procedures for measuring BP and pulse wave velocity (PWV)

Clinical BP was measured in compliance with guidelines (WHO-ISH 1999) [19], using a mercury sphygmomanometer and an appropriate cuff to the arm circumference, in patients at rest for 10 min (Korotkoff phase I for SBP and V for DBP). Three measurements were carried out and averaged for analysis. Pulse pressure was computed as PP = (SBP – DBP); and mean BP was computed as MBP = DBP + (PP/3).

Arterial stiffness was assessed by automatic carotid-femoral PWV measurement using Complior® device (Artech Medical, Pantin, France); the technical characteristics of this device have been described in details previously in [18]. Carotid-femoral PWV is calculated from the delay between the recorded proximal (carotid) and distal (femoral) feet of the digitized pressure waveforms, and the superficially measured distance separating the respective transducers. PWV was calculated on the ratio between distance and transit time: PWV (m/s) = distance (m)/transit time (s).

2.3. MS diagnosis

Recently, the NCEP-ATPIII[8] put forth a definition with the following criteria: BP $\geq 130/85$ mmHg; high-density lipoprotein-cholesterol (HDL-C) < 40 mg/dl (1.04 mmol/l) in men or < 50 mg/dl (1.30 mmol/l) in women; fasting glucose (FG) ≥ 110 mg/dl (6.1 mmol/l); triglycerides ≥ 150 mg/dl (1.69 mmol/l); and waist circumference (WC) > 102 cm in men or > 88 cm in women. Among the various definitions of MS [6–8], we chose the NCEP-ATPIII definition because it was ascertainable, most accepted and widely used in both clinical practice and epidemiological studies [20].

2.4. Statistical analysis

NCSS software (Number Cruncher Statistical Systems, Kaysville, UT, USA) was used for all statistical analyses. The quantitative variables were presented as mean values ± standard deviation (S.D.); the qualitative variables as absolute values and percentages. Comparison of each quantitative variable mean between MS patients (n = 186) and controls (n = 254) was carried using two-sided Student's t-tests for Gaussian distribution variables, Mann–Whitney U-test for the non parametric distribution variables, and Chi-square test for the qualitative variables. To assess simple interactions between different continuous or discrete parameters Pearson or Spearman rank correlation was computed, followed by a linear or logistic regression. A P-value < 0.05 was considered significant.

2.5. MS association with PWV

Multiple regression models adjusted with age, gender, smoking status, serum creatinine, and MS (model A) or with individual MS risk factor components such FG, SBP, triglycerides, HDL-C, and WC as quantitative variables (model B), were established to evaluate independent determinants of PWV in the overall population (n = 440). Because age and SBP were determinants of PWV, the analysis of covariance (ANCOVA) was used to assess MS effect on PWV. To study the association between age and MS effect on PWV we stratified the population into two sub-groups using as cut-off population age median (47 years). Multivariate models described above were also performed in each age group and adjusted with risk factors. In order to test interaction between age, SBP, MS and its effect on PWV, age was considered as two levels factor where age median (47 years) was the cut-off. SBP was defined as three levels factor (140–159, 160–179, and ≥ 180 mmHg). Both factors where included in the age-SBP-adjusted ANCOVA model.

Adjusted odd ratio was calculated as the antilogarithm of the β-coefficient of the logistic regression of MS with the two age groups corrected with age and SBP. Ninety-five percent confidence intervals (CI) around the adjusted odds ratios were estimated.

3. Results

3.1. Prevalence of MS and cardiovascular risk factors

Four hundred and fifty never-treated patients were pre-included in this study. Ten patients were excluded due to missing values. The global prevalence of MS was 42.3%. The study population of 440 patients was constituted from 59.8% Caucasian, 18.2% Hispanic, 13.9% Asian, and 10.1% African, Table 1 shows their anthropometric, metabolic and vascular characteristics. Significant differences between MS patients and their controls were noticed. The hypertensive MS group was 5 years older than the hypertensive control group, 83% of MS patients had hypertriglyceridemia, 82% had abnormal levels in HDL-C, 53% had high WC, 31% were obese with a BMI > 30 kg/m^2, and 22% had hyperglycemia; PWV was 1 m/s higher (Table 1). Five percent were frank diabetics (FG > 6.9 mmol/l), 82% of hypertensive diabetics had MS. This group of hypertensive diabetics was 5 years older than the MS group (55 ± 9 years) with a PWV of 12.2 ± 1.6 m/s.

Significant correlations (Table 2) between PWV, and age, BP, MS, and gender were found in the overall population.

3.2. MS impact on arterial stiffness

In order to evaluate confounding factors (age, gender, smoking, MS compounds) which may modify MS effect on PWV a multivariate regression was performed. Multivariate regression (R^2 = 0.38) detected SBP ($P < 10^{-3}$) and age ($P < 10^{-3}$) as independent determinants of PWV (Table 3). Replacement of SBP by pulse pressure (PP) and mean blood

Table 1
Clinical characteristics and hemodynamic parameters of patients with or without MS

Variables	Without MS (n = 254)	With MS (n = 186)	Total population (n = 440)	P-value (MS v/s control)
Age (years)	45 ± 13	50 ± 11	47 ± 12	$<10^{-3}$
Woman gender (%)	40.6	51.6	45.2	0.02
BMI (kg/m^2)	25.7 ± 3.5	27.8 ± 3.8	26.6 ± 3.8	$<10^{-3}$
WC (cm)	86.7 ± 10.3	93.8 ± 10.8	89.7 ± 11.1	$<10^{-3}$
Men	91.4 ± 8.7	97.8 ± 9.61	93.8 ± 9.5	$<10^{-3}$
Women	79.9 ± 8.65	90.1 ± 10.4	84.8 ± 10.8	$<10^{-3}$
FG (mmol/l)	5.1 ± 0.75	5.6 ± 1.1	5.3 ± 0.95	$<10^{-3}$
Triglycerides (mmol/l)	1.4 ± 0.66	2.3 ± 0.8	1.79 ± 0.86	$<10^{-3}$
HDL cholesterol (mmol/l)	1.34 ± 0.4	1.02 ± 0.4	1.21 ± 0.43	$<10^{-3}$
Men	1.3 ± 0.38	0.91 ± 0.22	1.15 ± 0.38	$<10^{-3}$
Women	1.4 ± 0.4	1.12 ± 0.49	1.26 ± 0.47	$<10^{-3}$
Serum creatinine (μmol/l)	83.8 ± 16	83.7 ± 17	83.7 ± 17	NS
SBP (mmHg)	155 ± 14	160 ± 15	157 ± 15	$<10^{-3}$
DBP (mmHg)	99 ± 6	100 ± 7	100 ± 7	NS
MBP (mmHg)	118 ± 7	120 ± 8	119 ± 7	$<10^{-3}$
PP (mmHg)	56 ± 14	60 ± 15	58 ± 15	0.0011
Heart rate (bpm)	73 ± 10	75 ± 10	74 ± 10	NS
PWV (m/s)	10.9 ± 2.2	11.9 ± 2.4	11.3 ± 2.3	$<10^{-3}$

PWV: pulse wave velocity, DBP: diastolic blood pressure, SBP: systolic blood pressure, PP: pulse pressure, MBP: mean blood pressure, HDL-cholesterol: high-density lipoprotein-cholesterol.

Table 2
Correlations between PWV; MS as a binary vector (controls = 0, MS patients = 1) and anthropomorphic, metabolic and BP parameters

Variables	PWV (m/s)	MS
PWV (m/s)	1	0.2***
Age (years)	0.59***	0.19***
Gender	0.107*	0.109*
WC (cm)	0.11***	0.32***
BMI (kg/m^2)	0.27***	0.27***
Heart rate (bpm)	–0.087	0.04
DBP (mmHg)	0.05	0.07
SBP (mmHg)	0.3***	0.18***
PP (mmHg)	0.28***	0.15**
MBP (mmHg)	0.18***	0.16***
FG (mmol/l)	0.079	0.27***
HDL-cholesterol (mmol/l)	–0.06	–0.38***
Serum creatinine (μmol/l)	0.05	–0.003
Triglycerides (mmol/l)	0.16***	0.54***

* $P < 0.05$ ** $P < 0.01$ ***$P < 0.001$ PWV: pulse wave velocity; DBP: diastolic blood pressure; SBP: systolic blood pressure; PP: pulse pressure; MBP: mean blood pressure; HDL-cholesterol: high-density lipoprotein-cholesterol.

pressure (MBP) did not modify the relationship. Triglycerides had an independent significant effect on PWV ($P = 0.04$).

Moreover this multivariate regression showed an independent effect ($P = 0.01$) of MS on PWV in the overall population. The ANCOVA analysis (Table 4) showed the same effect of MS on PWV in the studied population ($P = 0.047$) after age and SBP adjustment. Population was divided into two subgroups according to the median age value (47 years). Effect of MS on PWV was not significant in the young population ($P = 0.998$) but markedly increased after 47 years ($P = 0.0047$) where the prevalence of SBP-adjusted MS is higher (OR 2.0, 95% CI 1.2–3.4). Global prevalence of MS was 32.2% in lower mid-age population and 52% in the upper mid-age population. No interaction was found between age and MS or SBP in global population, which shows the independent effect of these three risk factors on PWV.

Fig. 1 shows a statistically significant increase ($P = 0.015$) of PWV with age in the upper mid-age MS population (12.8 ± 2.2 m/s) compared with its controls (12.05 ± 2.13 m/s) which does not exist in the younger population (MS: 10.4 ± 2.04 v/s controls: 10.1 ± 1.82 m/s). This increase was analyzed in Fig. 2 which shows a significant increase ($P = 0.034$) of PWV proportionally to MS risk factor number only in the older population. Multivariate models and ANCOVA confirm that MS ($P = 0.047$), SBP ($P < 10^{-3}$), and age ($P < 10^{-3}$) are only prevalent aortic stiffness risk factors in older patients whereas only age ($P < 10^{-3}$) is prevalent in young patients.

Table 3
Multiple regression models with PWV as dependent variable and as independent variables age, gender, smoking, serum creatinine and MS in model A or SBP, HDL-cholesterol, fast glucose, and triglycerides in model B

Variables	Model A *P*-value	Model A standardized regression coefficient	Model B *P*-value	Model B standardized regression coefficient
R^2	0.36	–	0.38	–
MS	0.01	0.1	–	–
Age	$<10^{-3}$	0.6	$<10^{-3}$	0.55
Gender	NS	–0.02	NS	–0.01
Smoking	NS	0.01	NS	0.03
Serum creatinine	NS	0.02	NS	0.03
WC	–		NS	0.02
FG	–		NS	–0.06
Triglycerides	–		0.026	0.09
HDL-cholesterol	–		NS	–0.0001
SBP	–		$<10^{-3}$	0.15

NS: not significant; MS: metabolic syndrome; SBP: systolic blood pressure; HDL-cholesterol: high-density lipoprotein-cholesterol.

4. Discussion

4.1. Factors increasing arterial stiffness

Arterial stiffness has been described as an independent and powerful predictor of morbi-mortality [21,22]. In this study we used PWV as an arterial stiffness marker to detect the impact of MS on large arteries remodeling.

Our overall population was hypertensive with no discrepancies except for BP. On the other hand the MS group (42% of the population) showed discrepancies, respectively, for BP components (especially SBP), triglycerides, HDL-C and WC in women. Therefore increase of PWV was strongly correlated with these risk factors. As the majority of hypertensive diabetics had metabolic alterations with high arterial stiffness it would be urgent to take care of these patients at an early insulin resistance stage.

Table 4
ANCOVA showing an effect of the MS on PWV adjusted with age and SBP

Variables	18–47 years ($N = 217$)	48–73 years ($N = 223$)	Population ($N = 440$)
MS	NS	0.0047	0.047
Age	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$
SBP	NS	0.0019	0.001

NS: not significant, SBP: systolic blood pressure.

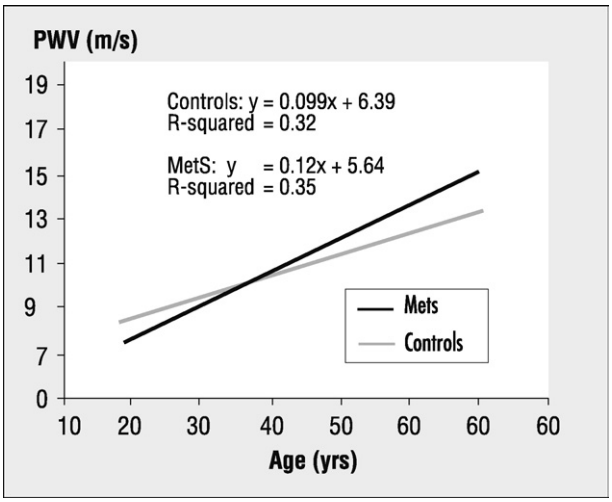

Fig. 1. Linear regression between PWV and age for MS patients and their controls. A high effect of MS on PWV ($P = 0.015$) may induce early arterial aging.

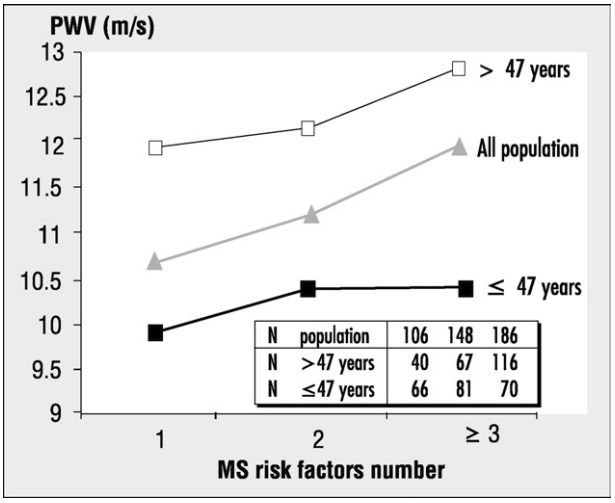

Fig. 2. Mean PWV per number of factors in older population (> 47) and young population (≤ 47). PWV is associated with risk factors number in all population ($P < 0.001$) especially in the older population ($P = 0.03$).

4.2. MS an arterial ageing factor

Ageing and SBP have been described as major causes of arterial stiffness [23,24], MS is also prevalent in 44% of people older than 50 years. But it is the first time that it has been shown that hypertensive MS patients have an increase of arterial stiffness independently from ageing and SBP within four different ethnic groups knowing that Caucasians constituted the biggest proportion. This strong association is probably caused by the increase of MS risk factors with age.

To take in consideration the different ethnic groups of the study population as well as the different risk factors effect, we confirmed our results by repeating the statistical analysis with a modified WC NCEP-ATPIII diagnosis for the Asian subpopulation [25]; WC > 90 cm in men or > 80 cm in women. The previous results were confirmed after WC correction with a decrease of PWV-MS impact in overall ($P = 0.038$) and young ($P = 0.8$) populations and an increase in elderly patients ($P = 0.028$). Global prevalence of MS increased from 42.3% to 43.9% after 47 years (OR = 2.2, 95% CI 1.3–3.7). Moreover after modifying MS diagnosis as advised by the America Heart Association and the National Heart, Lung, and Blood Institute Scientific Statement (AHA/NHLBI) [7] corrected MS effect on arterial stiffness became only statistically significant in patients over 47 years old. This largely confirms that our findings are independent from the modification of the MS diagnosis criteria in the NCEP-ATPIII definition.

Studies previously showed a correlation between MS as defined by the NCEP-ATPIII and PWV in specific populations. Scuteri et al. [15] showed in untreated and treated normalized hypertensives a 16% increase of the arterial stiffness index in MS patients followed up for 1 year. Schillaci et al. [16] showed a relation between MS and PWV in untreated hypertensive patients where diabetics were excluded, but no correlation between MS and BMI was observed within the study population. In our population, PWV was 9% higher in MS patients. Recently, Mule et al. [17] described this association in a small untreated normalized hypertensives without diabetes mellitus. But this association disappeared after correction with a renal function factor (albumin excretion rate). It was not the case in this study where the impact of MS on arterial stiffness was higher independently from renal function (serum creatinine level). Thus, even in comparison with different populations with less MS patients and different techniques for PWV computing, somehow our study showed that MS impact on PWV is concordant with both previous studies. This confirms that arterial structural and functional alterations are caused by the MS factors [26,27].

In this investigation, the comparison carried between MS and hypertensive control patients in mid-aged population at variance with other studies conducted in healthy young adults [28] or mid-age [29] did not show a statistical difference in PWV. These contradictory results may be explained by the difference between population characteristics (hypertensive patients, volunteers, …) or/and the different methods used to assess PWV (ankle-brachial, carotid-femoral, oscillometric, …). Moreover, this may explain the weak impact of MS in hypertensive young/mid-age population on PWV where SBP is a more physiopathological determinant of arterial stiffness than metabolic factors. Thus, more investigations are needed to confirm that the impact of MS in the younger population could be observed only in normotensive subjects where the weight of MS is independent from BP level.

Regarding MS topology, neither hyperglycemia nor global obesity were the main components of the MS but high BP, and hypertriglyceridemia were detected as independent significant factors of aortic stiffness in the multiple regression models. These results are more general than Tremblay et al.'s [30] results in Caucasian male patients. Nevertheless, these findings have some limitations due to the exclusion of obese having a BMI ≥ 35 kg/m^2, and uncontrolled diabetes or diabetes with fasting glycemia > 10 mmol/l. It was necessary to exclude these patients in order to avoid bad PWV measurements for obese and diabetics. Current assumptions [31] emphasize the role of oxidative stress, inflammation and plasma free fatty acids (abdominal obesity) on the blockade of insulin signal transduction which lead to insulin resistance, a promoter of the MS.

5. Conclusion

In conclusion, MS increases arterial stiffness in untreated hypertensives. After middle age, high levels of triglycerides associated with other factors induce insulin resistance and lead to noticeable arterial stiffness. MS patients over 50 years old have high PWV correlated with MS risk factors number increase, which may induce an early arterial ageing.

As aortic stiffness and MS are well-known as high morbi-mortality risk factors [32], it remains to assess the link between the respective roles of stiffness and metabolic abnormalities associated to insulin resistance in mortality of hypertensive patients.

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