Oxidative Stress, Uric Acid, Vascular Inflammation in Non-Smoking Metabolic Syndrome Patients

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***Abstract*—** Substantial evidence states that serum uric acid is an important, independent risk factor for cardiovascular and renal disease especially in patients with hypertension, heart failure, or diabetes, relative to the oxidative stress that alters the plasma lipoprotein profile, the coagulative parameters, the endothelium and the cell membranes, but this is not supported by large scale clinical studies. There is increasing evidence that inflammation and endothelial dysfunction are the most important pathogenic pathways explaining the propensity to atherosclerosis and its complications in metabolic syndrome. Most adipocytokines and proinflammatory biomarkers (adiponectin, cell adhesion molecules, TNF-α, IL, CRP) are elevated in the serum and vessel walls of patients with metabolic syndrome, being positive predictors for cardiovascular events.
Aims: To investigate uric acid, oxidative stress, hs C-reactive protein and classical cardiovascular risk factors, in a never treated, non-smoking hypertensive adult patients group (age: 56,9±6,62, sex: m/f=14/22, waist: 93,2±20,3 Kg, ABP: 154.5±14/91.5±8.26 mmHg) with/without MetS vs age-, sex- matched control group.
Methods: The concentration of serum and erythrocyte superoxiddismutase (SOD), catalase (CAT) and malonaldialdehyde (MDA) were analysed by spectrofotometry. All the other risk factors (uric acid, fasting glucose, lipid profile) were assessed by validated standard procedures. High sensitive C-reactive protein (hs CRP) has been performed by a sandwich ELISA method.
Results: Plasma levels of oxidative stress parameters determined and hsCRP are significantly higher than the control group ($p<0.0001$). Oxidative stress markers in non-smoking hypertensive group are strongly correlated ($r>0.7$) with ABP values, the number of criteria for MetS, waist, BMI and hsCRP, they have an average correlation with age, weight, SCORE algorithm and are not correlated with fasting plasma glucose, triglyceride, HDL-C. The coefficient of determination is significantly increased between the number of criteria for the MetS and oxidative stress parameters. Uric acid levels are correleted on average with weight, waist, BMI, average BP, diastolic BP and have a weak correlation with hs-PCR and oxidative stress parameters. Level of hsCRP activity is strongly correlated with waist, the number of criteria for MetS, oxidative stress markers, SCORE algorithm and has an average correlation with BMI, TG, HDL-C.
Conclusions: Increase oxidative stress activity and CRP levels are associated with MetS. When applying multiple linear regression, adjusted for sex, age, classical cardiovascular risk factors, arterial blood pressure becomes a powerful and independent determinant factor of oxidative stress parameters; weight and waist are a powerful and independent determinant factors of hs-CRP values.

***Keywords*—**cardiovascular risk factors, high sensitive C-reactive protein, metabolic syndrome, oxidative stress, uric acid

I. INTRODUCTION

Hypertension and diabetes are major cardiovascular risk factors greatly responsible for mortality and cardiovascular morbidity. Prevalence of hypertension in the diabetic population is two times higher than in the non-diabetic population. On the other hand hypertension (HTA) is a strong predictor for developing diabetes (DM). Up to 75% heart disease conditions in diabetics can be attributed to hypertension. The most common pathogenic element in hypertension and diabetes is the endothelial malfunction which may severely disrupt the body's homeostasis by generating pro-aggregation, pro-coagulation and pro-inflammatory statuses, respectively. One of the pathogenic mechanisms that can explain this increased risk in diabetes is the imbalance between the pro-oxidants and the antioxidants, which results in the oxidative stress. Hyperglycaemia results in glucose auto-oxidation, non-enzymatic glycation and monocyte dysfunction, which lead to increased production of free radicals. This is

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further aggravated by the decreased levels of antioxidants and leads to oxidative damage [1], [2].

Strong experimental evidence indicates that increased oxidative stress and associated oxidative damage are mediators of renovascular injury in cardiovascular pathologies. An increase in the production of superoxide anion and hydrogen peroxide, the reduced nitric oxide synthesis and the decreased bioavailability of antioxidants have been demonstrated in experimental and human hypertension.

Vascular oxidative stress has been demonstrated in spontaneous (genetic) and experimental hypertension. Spontaneously hypertensive rats (SHR) and stroke-prone SHR, two genetic models that develop hypertension spontaneously, exhibit increased NAD(P)H driven •O2 generation in resistance (mesenteric) and conduit (aortic) vessels. [6], [8], [13], [14]. This is associated with an over expression of the NAD(P)H oxidase subunit and enhanced oxidase activity [4], [7], [13], [15]. Oxidative stress in genetic hypertension involves enhanced NAD(P)H oxidase activity and dysfunctional endothelial nitric oxide synthase (uncoupled NOS) and is partly regulated by AT1 receptors.

Vascular oxidative stress has also been demonstrated in experimentally-induced hypertension, such as Ang II–mediated hypertension, Dahl salt-sensitive hypertension, lead-induced hypertension, obesity-associated hypertension, mineralocorticoid hypertension, and aldosterone-provoked hypertension [16], [17]. Activation of vascular NAD(P)H oxidase and xanthine oxidase and endothelial nitric oxide synthase uncoupling [9], [10], [14], [18], [19] have been implicated in amplification of •O2 generation in experimental hypertension.

A few clinical studies showed increased ROS production in patients with essential hypertension, renovascular hypertension, malignant hypertension, and pre-eclampsia [20]–[22]. These findings are generally based on increased levels of plasma thiobarbituric acid-reactive substances and 8-epi isoprostanes, biomarkers of lipid peroxidation and oxidative stress [5], [23]. Accumulation of ROS byproducts from oxidized genomic and mitochondrial DNA have also been found in hypertensive individuals [5]. Polymorphonuclear leukocytes and platelets, rich in •O2 sources, also participate in vascular oxidative stress and inflammation in hypertensive patients [24], [25]. Decreased antioxidant activity (SOD, catalase) and reduced levels of ROS scavengers (vitamin E, glutathione) may contribute to oxidative stress [5], [23]. Activation of the renin-angiotensin system has been proposed as a mediator of NAD(P)H oxidase activation and ROS production [3], [9]–[13]. In fact, some of the therapeutic BP-lowering actions of AT1-receptor blockers and angiotensin-converting enzyme inhibitors (ACEI) have been attributed to NAD(P)H oxidase inhibition and decreased ROS production [26], [27].

In normal individuals, insulin has been shown to suppress several pro-inflammatory transcription factors, such as the NF-kB and the activating protein-1 (AP-1) [28]. In the metabolic syndrome, the insulin-resistant state will determine a pro-inflammatory condition and, therefore, the inflammation could be the most important link between the pathogenesis of atherosclerosis and the intervention in some important cardiovascular risk factors, such as the obesity or the diabetes mellitus. CRP, an important pro-inflammatory marker, has recently been introduced as a new factor of the metabolic syndrome [29]. In obesity and metabolic syndrome, the adipose tissue produces adipokines, some of them with an important influence on inflammation: TNF-α, IL-6, IL-1β, leptin, adiponectin and resistin [30]. Insulin's resistance action on the lipid metabolism is associated with the increase in the free fatty acid (FFA) concentrations in plasma, resulting in the induction of oxidative stress and inflammation [31].

Nowadays, atherosclerosis, the main cause of coronary artery disease, is equally considered an inflammatory and a metabolic disease influenced both by the hereditary and the environmental factors. The atheromatous lesions contain immune cells (mast cells, T cells, macrophages) that when activated produce inflammatory cytokines. The hemodynamic profile, the retention of LDL in the arterial wall, and the oxidation of LDL may initiate an inflammatory response in the arterial wall [32]. The cytokines present in the atherosclerotic lesions promote a type 1 helper T (Th1) response, similar to delayed hypersensitivity, rather than a helper T type 2 (Th2) one. As a result, the most powerful pro-inflammatory cytokines are CRP and IL-6, and from the 2 cytokines with the most demonstrated anti-inflammatory properties are the interleukin-10 (IL-10) and the transforming growth factor β (TGF-β), respectively [33], [34].

CRP was the most studied marker of inflammation in cardiovascular diseases and it was revealed to be an independent predictor of risk for myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death [47].

High serum uric acid (SUA) levels have been reported to be a risk factor for coronary heart disease [36] and are frequently observed among individuals with hypertension and type II diabetes. Since SUA level is highly related to obesity [37], which is in turn associated with risk of hypertension and type II diabetes [38], [39], the causal pathway may presumably exist between obesity and risk of hypertension and type II diabetes. Therefore, the association between SUA level and risk of hypertension and type II diabetes and the effect of obesity on this association are of considerable interest.

II. MATERIALS and METHODS

A prospective study of 36 newly diagnosed, never treated, non-smoking patients with metabolic syndrome were recruited for this study. Anthropometrical, biochemical and hormonal parameters were determined. Blood pressure was recorded. The anthropometrical measurement included waist circumference (WC) and body mass index (BMI). BMI was computed as a ratio of weight to the square of height (kg/m2). Waist circumference was taken at the midpoint between the lowest rib and the iliac crest. Blood pressure was measured with a mercury sphygmomanometer fitted with a correct cuff size. The protocol included three measurements; the mean of all 3 measurements was used as systolic and diastolic blood pressure. Subjects were asked to fast for 12 h before the blood sampling that was collected around 7.00 a.m. Fasting plasma

glucose, serum triglycerides, serum HDL and LDL, total cholesterol, uric acid, fibrinogen, were measured enzymatically. High sensitive C-reactive protein (hs CRP) has been performed by a sandwich ELISA method (IBL International GMBH). The concentration of serum and erythrocyte superoxiddismutase, catalase and malonaldialdehyde were analysed by spectrofotometry. According to the International Diabetes Federation the metabolic syndrome is diagnosed for a person with central obesity plus at least two of the following criteria: raised TG level ≥ 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality, reduced HDL cholesterol < 40 mg/dL (1.03 mmol/L*) in males , < 50 mg/dL (1.29 mmol/L*) in females, or specific treatment for this lipid abnormality, raised blood pressure ≥ 130 / 85 mm Hg, or treatment of previously diagnosed hypertension, raised fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes. The results were compared with measurements from the control group, consisting of 15 healthy persons matched for age and sex (free from the metabolic syndrome, hypertension or dislipidemia). Rest and stress test electrocardiograms were performed to exclude coronary artery disease.

We have calculated the 10-year risk of cardiovascular death using the risk chart for a high risk population: The Systematic Coronary Risk Evaluation (SCORE) algorithm.

All participants have given informed written consent and the study was conducted in accordance with the Helsinki Declaration and approved by the local Ethics Committee.

Statistical analysis: data are given as mean ± standard deviations. Statistical analysis has been performed using the *Microsoft Office Excel* 2007+Analyse-it software, applying parametric and non-parametric tests (one-way breakdown ANOVA, Mann-Whitney U test, Spearman correlation). The results are considered statistical significant when two-tailed $p < 0.05$, α=95%.

III. RESULTS and DISCUSSION

There were significant differences for the recorded parameters between the patients with metabolic syndrome and those from the control group. The group characteristics (age, weight, waist, systolic and diastolic blood pressure, number of criteria for MetS) and the routine blood parameters (fasting plasma glucose, cholesterol, HDL, LDL, TG) for the two studied groups are presented in table I.

Table I: Anthropometric parameters and blood pressure for the two studied groups

Parameters	Control Group (n=15)	Hypertension Group (n=36)
Age (years)	58.33±6.18	56.91±6.62
Sex (F/M)	7F/8M	22F/14M
Weight (kg)	82.3±10	93.22±20.37
WC (cm)	88.13±9.87	108.36±12.28
BMI (kg/m²)	26.77±2.73	32.46±5.23
Systolic blood pressure (mmHg)	Normal range	154.57±14
Diastolic blood pressure (mmHg)	Normal range	91.52±8.26
Average blood pressure (mmHg)	Normal range	112.52±7.56

Table II: The blood parameters for the two studied groups

Parameters	Control Group	Hypertension Group
Fasting plasma glucose (mg/dL)	Normal range	135.33±76.48
Cholesterol (mg/dL)	Normal range	225.83±45.52
HDL-c (mg/dL)	Normal range	49.55±15.38
LDL-c (mg/dL)	Normal range	137.02±37.99
TG-c (mg/dL)	Normal range	192,72±116.49
Serum uric acid (mg/dL)	Normal range	4.83±1.56
hs-CRP (mg/ml)	Normal range	2.93±0.61
Fibrinogen (mg/ml)	Normal range	331.52±40.53

The biochemical parameters indicating the blood redox status for the two studied groups are listed in table III.

Table III: The biochemical parameters indicating the blood redox status

Parameters	Control Group	Hypertension Group	p-value
Serum MDA (mmol/ml)	3.69±0.43	9.32±0.47	< .0001
Erythrocyte MDA (mmol/ml)	0.85±0.07	0.7±0.06	< .0001
Serum SOD (U/g Hb)	78.49±4.36	401.299±21.66	< .0001
Erythrocyte SOD (U/g Hb)	3764.44±289.03	792.66±47.22	< .0001
Serum CAT (mmol/g)	2.17±0.17	0.798±0.058	< .0001
Erythrocyte CAT (mmol/g)	11±0.61	149.52±7.08	< .0001

Age was similar to both groups. For all other parameters there was a statistical significant difference in the MetS group in comparison with the control. Taking into consideration the numbers of the inclusion criteria the MetS group consisted as it follows of: 10 patients with 3, 11 patients with 4, and 7

patients with 5 criteria, respectively. From the 36 patients recruited: 2 meet only the waist criteria, and 6 of them only two criteria. All these patients were diagnosed with HTA that was not previously treated. Patients from the control group had normal values for blood parameters; any noticeable modification would mean exclusion from the group.

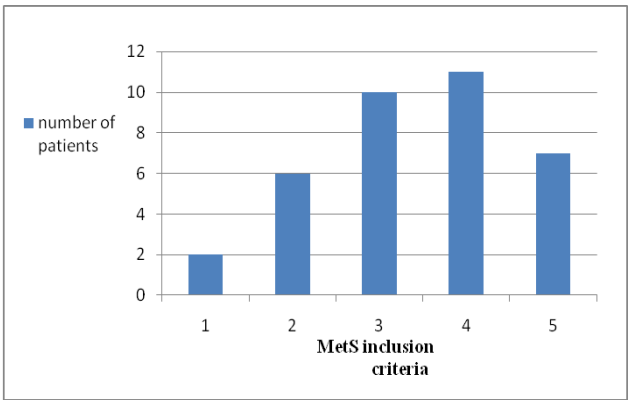

Fig.1 Distribution of patients depending on MetS inclusion criteria

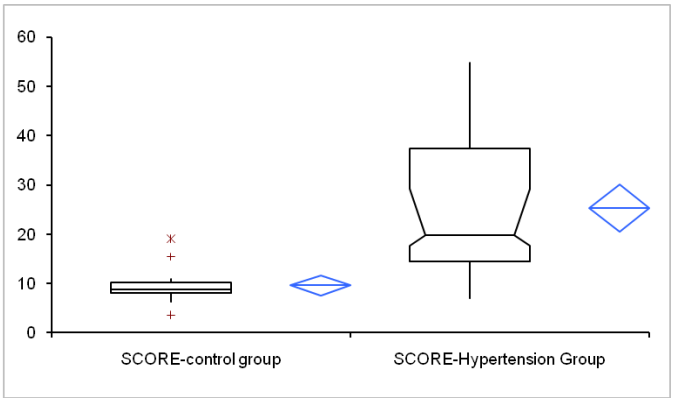

Fig.2 SCORE algorithm for control and hypertensive groups

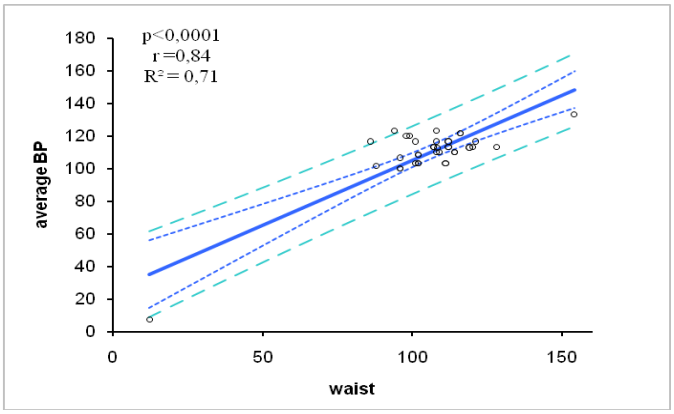

Fig.3 The correlation between waist and average BP

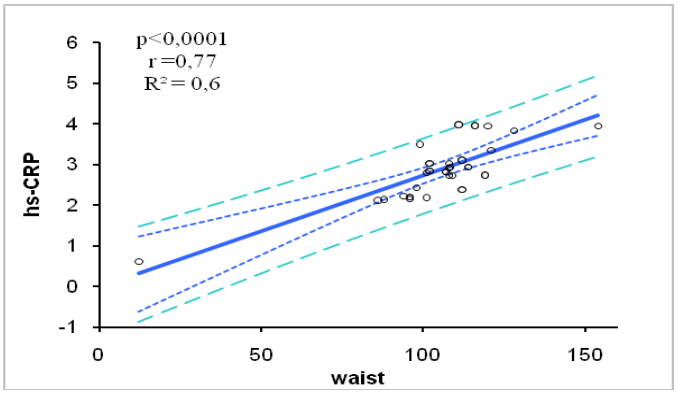

Fig.4 The correlation between waist and hs-CRP

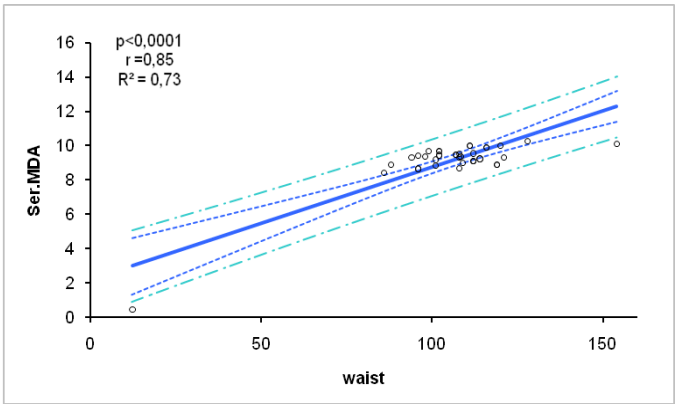

Fig.5 The correlation between waist and serum MDA

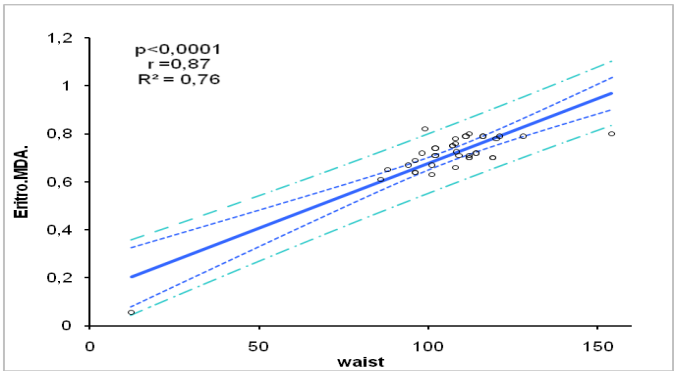

Fig.6 The correlation between waist and erythrocyte MDA

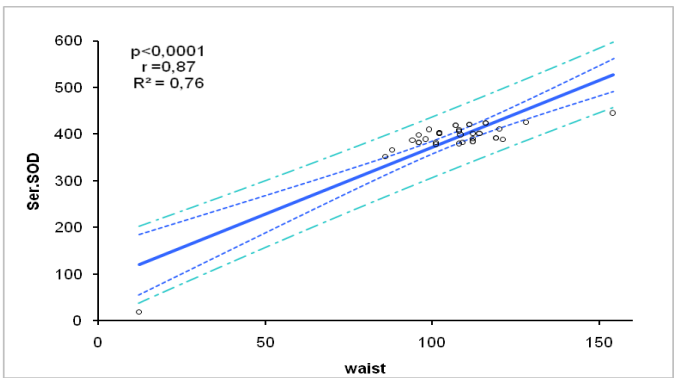

Fig.7 The correlation between waist and serum SOD

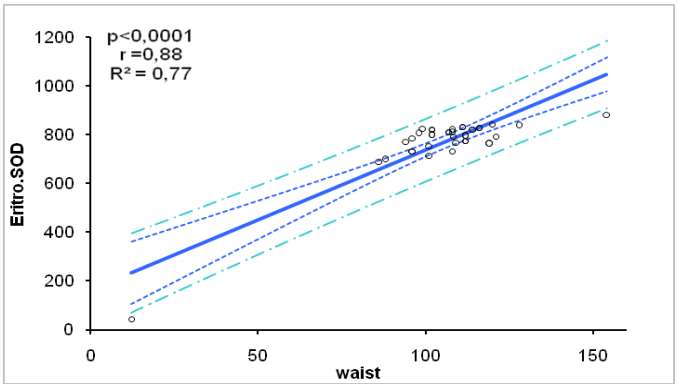

Fig.8 The correlation between waist and erythrocyte SOD

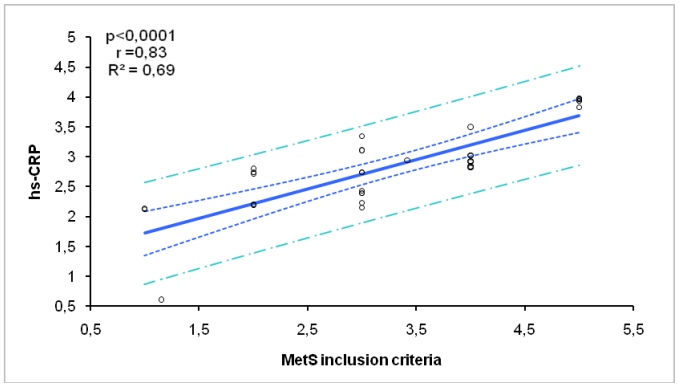

Fig.12 The correlation between MetS inclusion criteria and hs-CRP

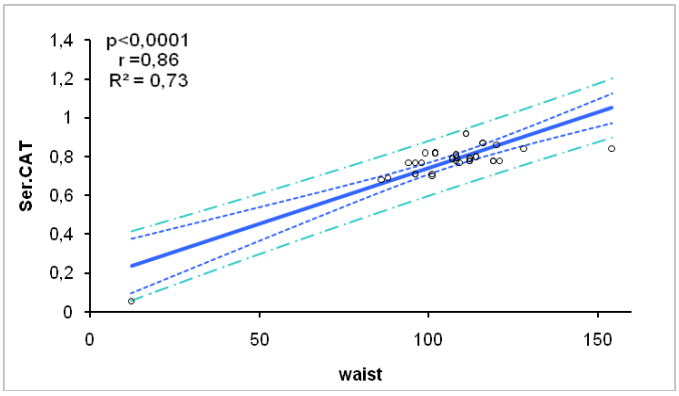

Fig.9 The correlation between waist and serum CAT

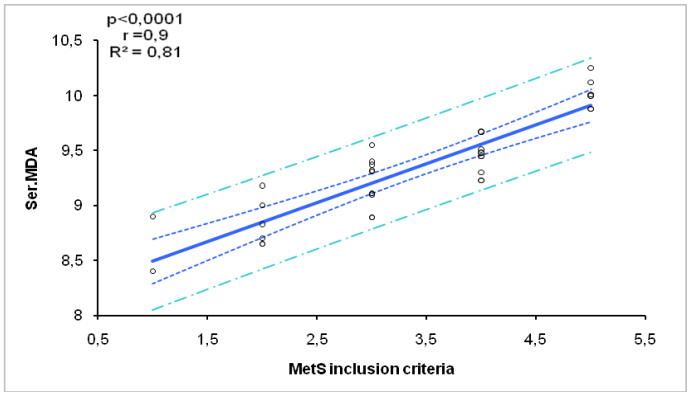

Fig.13 The correlation between MetS inclusion criteria and serum MDA

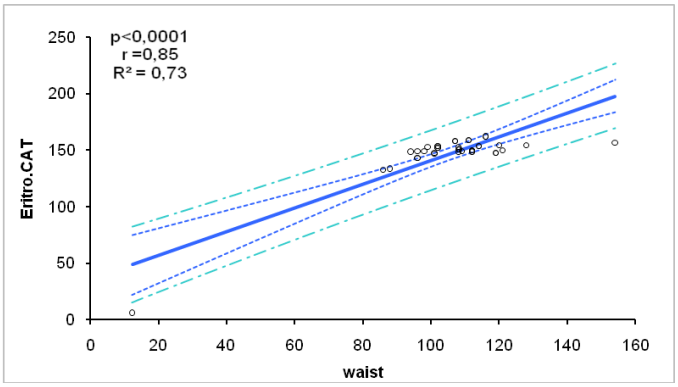

Fig.10 The correlation between waist and erythrocyte CAT

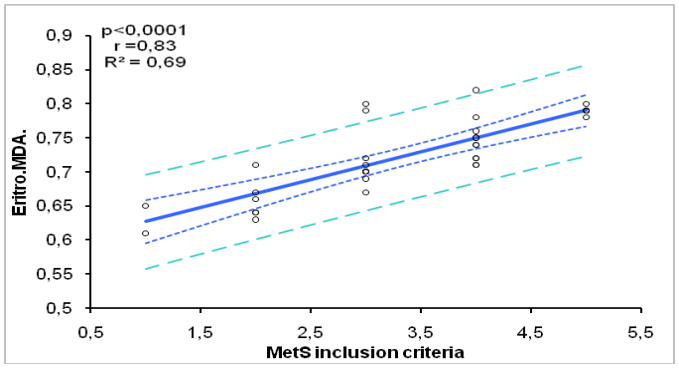

Fig.14 The correlation between MetS inclusion criteria and erythrocyte MDA

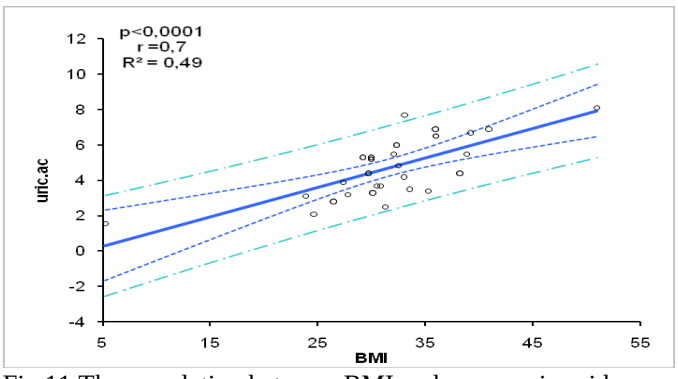

Fig.11 The correlation between BMI and serum uric acid

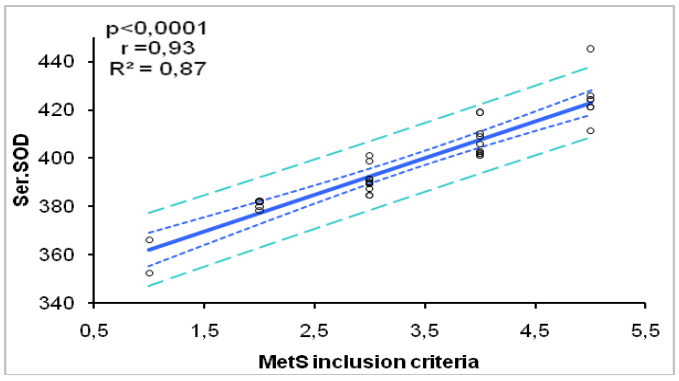

Fig.15 The correlation between MetS inclusion criteria and serum SOD

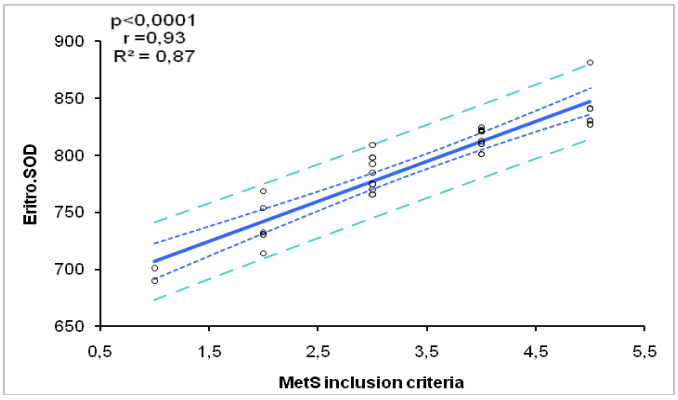

Fig.16 The correlation between MetS inclusion criteria and erythrocyte SOD

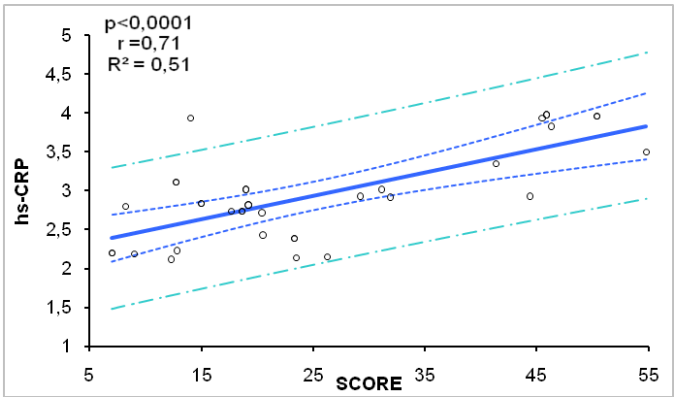

Fig.19 The correlation between SCORE algorithm and hs-CRP

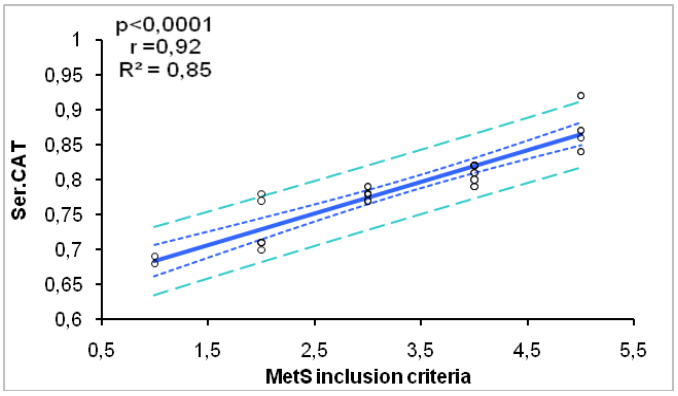

Fig.17 The correlation between MetS inclusion criteria and serum CAT

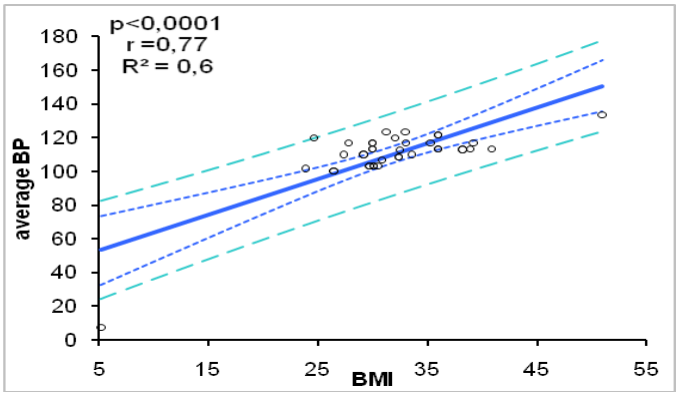

Fig.20 The correlation between BMI and average BP

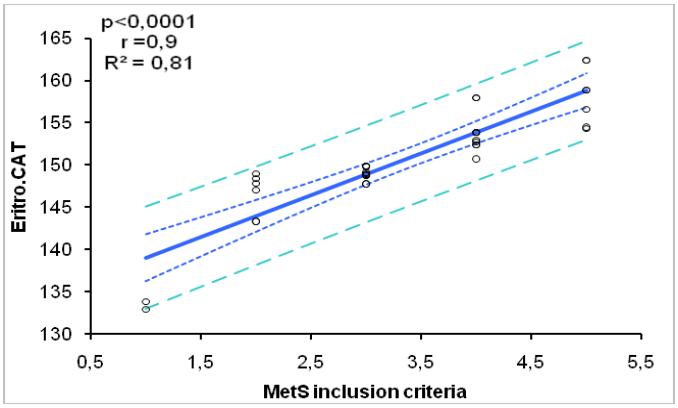

Fig.18 The correlation between MetS inclusion criteria and erythrocyte CAT

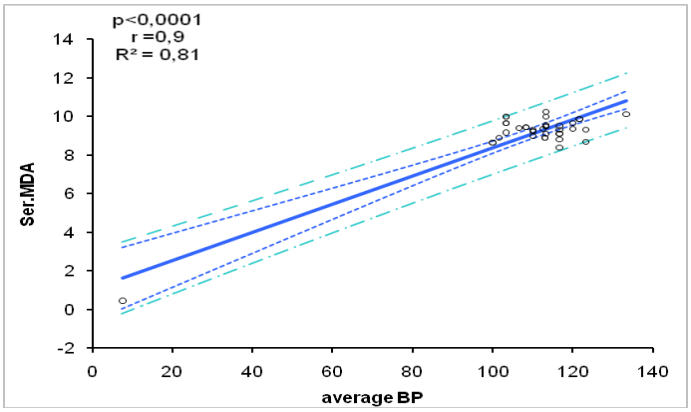

Fig.21 The correlation between average BP and serum MDA

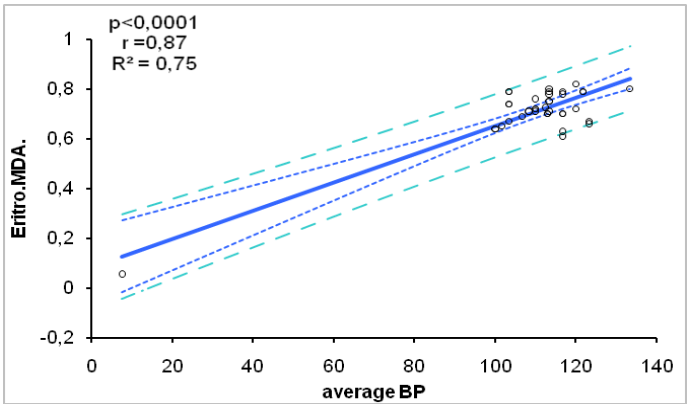

Fig.22 The correlation between average BP and erythrocyte MDA

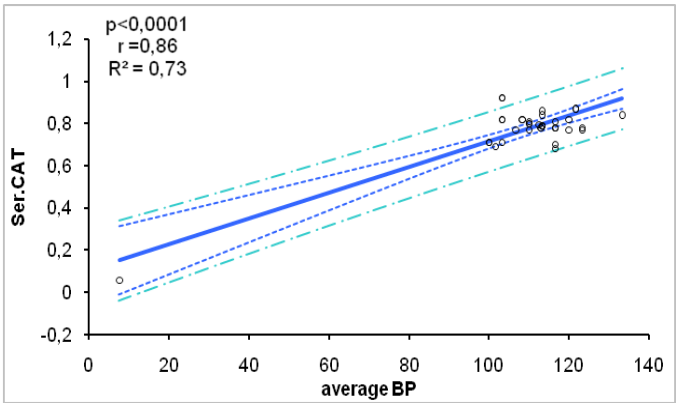

Fig.25 The correlation between average BP and serum CAT

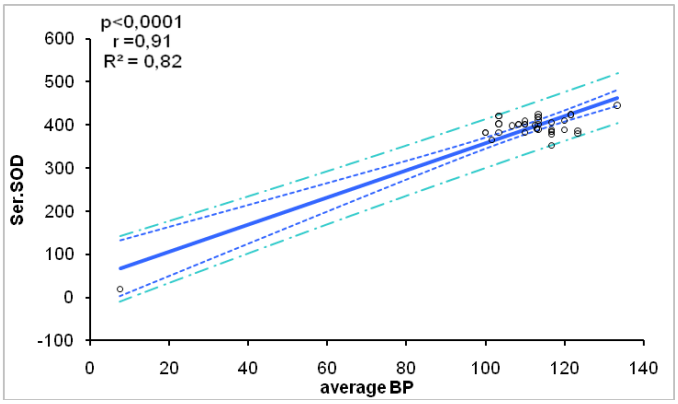

Fig.23 The correlation between average BP and serum SOD

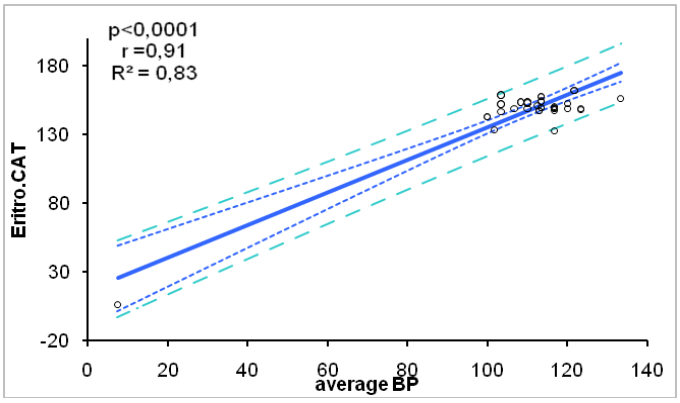

Fig.26 The correlation between average BP and erythrocyte CAT

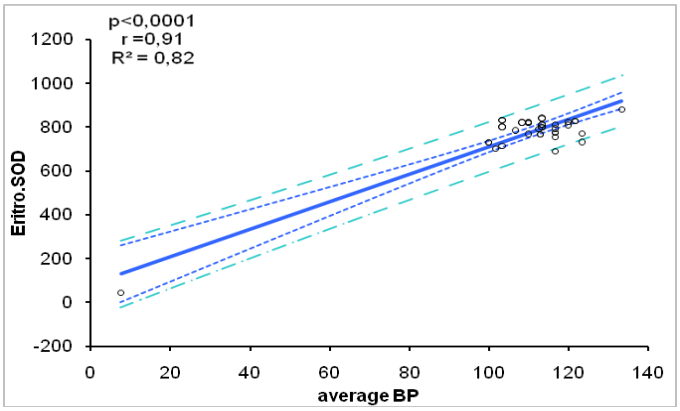

Fig.24 The correlation between average BP and erythrocyte SOD

Plasma level of oxidative stress parameters analysed for patients with/without MetS, non-smoking and HBP are significantly higher than the control group ($p<0,0001$, $\alpha=0,05$); they are strong correlated with ABP values (systolic, diastolic, average), the number of inclusion criteria in MetS, waist, BMI the parameters of lipid profile and inflammatory status (only hs-CRP) ($r>0,7$); have an average correlation (r: 0,5-0,7) with the age, weight, SCORE algorithm; have a weak correlation with fasting plasma glucose, triglyceride, HDL-C; the determination coefficient (R^2) is significantly increased between the number of criteria for MetS, waist, ABP and the parameters of the oxidative stress.

Level of hs-CRP activity is strongly correlated with waist, the number of criteria for MetS, oxidative stress markers, SCORE algorithm and has an average correlation with BMI, TG, HDL-C. hs CRP levels are strongly influenced by waist, weight.

Uric acid levels are correlated on average with weight, waist, BMI, average BP, diastolic BP and have a weak correlation with hs-PCR and oxidative stress parameters.

IV. CONCLUSIONS

In this study we found significant differences between the parameters recorded for patients with and without

metabolic syndrome, respectively; these results support the concept that this group of patients have a higher cardiovascular risk.

Increased oxidative stress activity and hs-CRP levels are associated with MetS. Applying multiple linear regression, adjusted for sex, age, classical cardiovascular risk factors, arterial blood pressure is a powerful and independent determinant factor of oxidative stress parameters; weight and waist are a powerful and independent determinant factor of hs-CRP values.

A multimarker strategy may be useful in evaluating the cardiovascular status in this type of patients.

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