Markers of Redox Imbalance in the Blood of Hypertensive Patients of a Community in Northeastern Brazil

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Abstract

Background: **Recent studies describe the participation of reactive oxygen and nitrogen species in hypertension.**

Objective: **To identify the redox imbalance in the blood of hypertensive.**

Methods: **Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione (GSH), vitamin C, transferrin, ceruloplasmin, malondialdehyde (MDA) and carbonyl group were quantified in the blood of 20 hypertensives and 21 controls. The individuals had a Body Mass Index of ≥ 18.5 and ≤ 30 kg/m², glycemia ≤ 100 mg/dL, serum cholesterol ≤ 200 mg/dL, and were nonsmokers, non-pregnant and non-lactating women, non-users of alopurinol and probucol, with hypertensives on antihypertensive medication. All individuals underwent a preparatory period of 4 weeks without alcohol, vitamin supplements, dexamethasone and paracetamol.**

Results: **Reduced levels of CAT (p 0.013), GSH (p 0.003) and MDA (p 0.014), and high levels of GPx (p 0.001) and ceruloplasmin (p 0.015) were obtained in the hypertensive group compared with controls. A positive correlation between systolic pressure and MDA in hypertensive and diastolic pressure and CAT in controls was obtained.**

Conclusion: **The data obtained suggest that the hypertensives were in redox imbalance, despite the possibly attenuating effect of their antihypertensive medication. (Arq Bras Cardiol 2011; 97(2) : 141-147)**

Keywords: **Hypertension; biological markers; antioxidants; oxidative stress; enzymes.**

Introduction

Hypertension has been the object of many studies due to its high prevalence and high impact on morbidity and mortality: population-based surveys conducted in various Brazilian cities indicate its prevalence in 22.3% to 43.9%[1].

Among the factors associated with the development of hypertension, an extremely important, complex and current one is the participation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in its pathogenesis. Hence, the oxidative hypothesis of hypertension is based on the fact that the vascular endothelium, the central organ within the scope of hypertension, is the site of a number of redox processes, mainly through the enzymes NAD(P)H oxidase, xanthine oxidase (XO), and endothelial nitric oxide synthase (eNOS), which act not only by increasing the production of superoxide radical anion ($O_2^{\bullet -}$) but also through mechanical forces that stimulate $O_2^{\bullet -}$ production. Overproduction of $O_2^{\bullet -}$ favors the reaction with nitric oxide ($^{\bullet}NO$) and forms peroxynitrite ($ONOO^-$), a particularly harmful reactive intermediary, since it is able to form hydroxyl radical ($^{\bullet}OH$) regardless of the presence of transition metal. Among other related phenomena, the diversion of $^{\bullet}NO$ from its vasodilatory function promotes the growth of endothelial cells and vasoconstriction[2-13]. Oxidative stress can be determined by means of redox balance biomarkers that are quantifiable in biological fluids[14].

The main purpose of this study was to quantify some antioxidants and markers of oxidative damage in the blood of a group of hypertensives and controls.

Methods

Selection of study participants

The individuals included in this study are residents of the city of Flexeiras, AL, Brazil, a small city covering an area of 316 square kilometers, with a population of 11,881, located in the Zona da Mata region of the state of Alagoas in northeastern Brazil, 60 kilometers from the state capital, Maceió. Most of the income of Flexeiras comes from the sugarcane monoculture, according to http://www.ibge.org.br

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Individuals

The participants of this study were selected from a sample of 433 out of the 803 hypertensives registered by the public health teams of the city of Flexeiras in 2005. They represented 53.92% of the hypertensives monitored by the local health service. All of the 433 hypertensives were evaluated from January to June 2005, based on anthropometric data (weight, height, waist circumference), clinical data (arterial pressure levels, diabetes diagnosis, use of medication), biochemical data (fasting glycemia, total cholesterol and triglycerides after 12 hours of fasting), and lifestyle (smoking, lack of exercising). Inclusion criteria were: (1) patients with hypertension[1]; (2) 40 to 60 years old; (3) not obese, with body mass index (BMI) $\leq$ 30 kg/m^2 and $\geq$ 18.5 kg/m^2; (4) with fasting glycemia of $\leq$ 100 mg/dL and serum cholesterol of $\leq$ 200 mg/dL; (5) non-menopausal, non-pregnant, non-lactating women not using contraceptives. Patients with diagnosis of diabetes mellitus, fasting glycemia of > 100 mg/dL, cholesterol > 200 mg/dL, users of alopurinol and probucol, and smokers were excluded.

A total of 63 non-hypertensive individuals (control group), volunteers, also residents of Flexeiras, signed the informed consent form and were subjected to the same selection criteria.

The protocols complied with the principles of the Declaration of Helsinki and the patients who met the selection criteria were included after reading and signing a written and informed consent form approved by the research ethics committee of the Federal University of Alagoas (UFAL), under process number 009991/2004-79, dated November 20, 2005.

Socioeconomic data

In addition to the aforementioned information, the individuals were surveyed in terms of social class, based on the Brazil Economic Classification criteria of the ABEP (Brazilian Association of Market Research Firms), per capita income and education level.

Preparation for blood collection

The individuals selected were instructed to stop using interfering medication such as vitamin and mineral supplements, paracetamol, dexamethasone and alcoholic beverages four weeks prior to drawing blood. During this period, the individuals were contacted systematically through home visits and phone calls to ensure that the preparatory phase was being followed.

Blood samples and analytical procedures

After 12 hours of fasting, blood samples were drawn and deposited into vacutainers in 3 aliquots of total blood: (1) 10 mL in heparin for analysis of antioxidant enzymes: superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT), glutathione (GSH), all of which in erythrocytes and carbonyl in plasma; (2) 5 mL in EDTA for hemogram; and (3) 5 mL, without anticoagulant, for uric acid, ceruloplasmin (CER), transferrin, malondialdehyde (MDA) and vitamin C readings in serum. Total blood was centrifuged at 3,000 rpm for 5 min. An aliquot of 500 μL of serum was stored in triplicate at a temperature of -20°C, while one aliquot of 500 μL of serum, one aliquot of 200 μL of plasma and four aliquots of 500 μL of plasma were stored in triplicate at a temperature of -80°C.

SOD, CAT and GPx activity were determined, respectively, according to the RANDOX-Ransod enzyme kit, the Aebi method, and Paglia and Valentine; GSH according to the Akerboom and Sies method; carbonyl according to the method of Levine; and MDA and vitamin C by HPLC-UV as described by Katepe. CER and transferrin were analyzed with the Spinreact kit. All of the methods used were described by Vasconcelos[14].

Statistical analysis

The statistical analysis initially involved the application of Kolmogorov-Smirnov's test to check the Gaussian distribution. To compare the groups, Student's *t* test, Pearson's chi-square (χ^2) and Fischer's test were used for the variables with normal distribution, and Mann-Whitney's and Spearman's test for the variables with asymmetric distribution. In all of the tests, $p < 0.05$ was adopted as statistically significant.

Results

General characteristics of the study population

Out of the 433 hypertensives, 24 (5.5%) met the selection criteria and 20 (4.6%) completed the protocol. As for the control group, out of the 63 volunteers studied, 21 (33.33%) met the selection criteria and completed the protocol. Therefore, the study was conducted with 20 hypertensives and 21 controls, whose demographic, socioeconomic, anthropometric and biochemical characteristics are listed in Table 1.

Table 1 - General characteristics of controls and hypertensive individuals

Variables	Hypertensive Individuals (n = 20)	Controls (n = 21)	p value
Age. y†	49.95 ± 6.99	45.85 ± 6.31	NS
Gender, M/F‡	14/6	15/6	NS
BMI, kg/m²†	26 ± 2.45	26 ± 2.94	NS
Waist, cm†	90.16 ± 8.02	93.25 ± 7.54	NS
SBP, mm Hg†	139.28 ± 11.41	113.33 ± 12.30	< 0.0001*
DBP, mm Hg†	95 ± 9.40	73.33 ± 8.87	< 0.0001*
Baseline glucose, mg/dL†	86 ± 10.14	81 ± 10.55	NS
Total cholesterol, mg/dL†	170.85 ± 13.20	151.01 ± 23.66	NS
Social class, C/D/E§//	8/10/2	8/8/3	NS
Schooling, 0/1/2§//	9/6/5	8/5/7	NS
Per capita income, US$ 1¶	234.76 ± 182.34	354.73 ± 207.12	NS
Smokers	0	0	-
Menopause	0	0	-

**P values denote differences between hypertensive and control; † Student's t test; ‡ Pearson's χ2 test; § Fischer's exact test; // CCEB criteria ; ¶ November 10. 2006. NS - not significant.*

Treatment with antihypertensive medication

The hypertensives were under antihypertensive therapy and regular users of antihypertensive medication (Table 2). In this group, 30% were users of diuretics, 25% used an ACE inhibitor, and 30% used an association of two medications.

Table 2- Antihypertensive drug treatment

Antihypertensive drug treatment	Medication use and dosage (mg)	Patients (n, %)
Diuretic	HCT†, 25 mg	6 (30%)
ACE‡ inhibitor	Captopril 25 mg	3 (15%)
	Captopril 50 mg	2 (10%)
Diuretic + ACE inhibitor	HCT 25 mg + Captopril 25 mg	4 (20%)
	HCT 50 mg + Captopril 50 mg	2 (10%)
Diuretic + ACE inhibitor + beta-blocker	HCT 25 mg + Captopril 25 mg + Atenolol 40 mg	1 (5%)
No drug		2 (10%)
Total patients		20 (100%)

†HCT- Hydrochlorothiazide; ‡ ACE - Angiotensin-Converting Enzyme.

Antioxidants and biomarkers of oxidative damage

Hypertensive individuals presented reduced blood levels of SOD, CAT, GSH, transferrin and MDA and high blood levels of GPx, ascorbate, CER and carbonyl compared to the controls. However, only the blood levels of CAT, GSH and MDA (reduced) and GPx and CER (increased) showed significant differences (Table 3).

Correlation among pressure levels and Biomarkers of Oxidative Damage

Pearson and Spearman correlation tests had revealed a positive correlation between SBP and MDA ($r = 0.44$ e $p = 0.04$) in the study population, and between PAD and CAT ($r = 0.54$ and $p = 0.01$) into the controls. Among the biomarkers, a negative correlation was found between MDA and GPx in both groups ($r = -0.63$ and $p = 0.003$ in the study population and $r = -0.63$ and $p = 0.004$ into the controls).

Discussion

An epidemiological study found a positive association between increased oxidative stress and reduction of the antioxidant status with cardiovascular risk factors in the general population[15,16]. Experimental and clinical studies

Table 3 - Antioxidants and biomarkers of oxidative stress in the study population

Groups of Biomarkers	Study population and values obtained (mean ± SD and median)		p value
	Hypertensives (H) (n = 20)	Controls(C) (n = 21)	
Antioxidant enzymes			
SOD (U/gHb) †	1,498.85 ± 575.04 1,470.00	1,649 ± 407.43 1,722.00	NS
CAT (KU/gHb) †	68.00 ± 32.83 67.24	102.08 ± 49.36 102.48	0.013*
GPx (U/gHb) ‡	20.51± 9.42 21.51	7.77 ± 9.60 2.00	0.0001*
Antioxidant of low molecular mass			
GSH (mM) ‡	5.33 ± 2.87 4.80	8.96 ± 5.19 7.00	0.003*
Uric acid (mg/dL) ‡	4.08 ± 1.33 3.80	3.49 ± 0.83 3.60	NS
Ascorbate (mmol/L) †	40.53 ± 12.93 37.63	34.58 ± 9.55 32.00	NS
Transport proteins $Fe^{+2/+2}$ $Cu^{+/+2}$			
Transferrin (mg/dL) †	189.60 ± 32.96 188.00	194.14 ± 38.42 189.00	NS
Ceruloplasmin (mg dL) ‡	38.60 ± 8.61 37.00	33.86 ± 3.97 33.00	0.015*
Biomarkers of oxidative damage			
Malondialdehyde (mmol/L) ‡	2.80 ± 4.49 1.42	8.51 ± 6.83 8.81	0.014*
Carbonyl (nmol/gPtna) ‡	2.13 ± 1.66 1.71	1.91 ± 1.42 1.67	NS

**P values denote differences between hypertensive and controls; † Student's t test; ‡ Mann-Whitney's test. NS - not significant.*

have demonstrated an increase in the production of reactive species in patients with essential hypertension[17-36] (Table 4). There is a high production of $O_2^{\bullet-}$ in hypertension that would lead to the formation of $ONOO^-$ (by reaction of $O_2^{\bullet-}$ with $^{\bullet}NO$), which occurs at a constant rate of 6.7×10^9 mol L^{-1} s^{-1} [16], while the dismutation reaction of $O_2^{\bullet-}$ by SOD occurs at a slower rate: 1.6×10^9 mol L^{-1} s^{-1} [4]. Furthermore, SOD activity is favored when the concentration of $O_2^{\bullet-}$ is low and that of SOD is high, which occurs only in physiological conditions[3]. These aspects would explain, in part, the prooxidant phenomena of hypertension[3,4,16]. Additionally, the activity of the antioxidant systems would be reduced, which would also favor the oxidative stress present in hypertension.

Clinical studies have demonstrated reduced antioxidant enzyme activity among hypertensives compared with controls[17,18], but it is not yet clear if this is a cause or a consequence of the hypertensive condition. Thus, oxidative stress in a chronic process such as hypertension could consume the reserves and impair antioxidant enzyme activity.

In view of the above, one would expect to see high levels of oxidative damage and low levels of antioxidants in hypertensives. However, in this study, the hypertensive group showed only lower levels of CAT and GSH antioxidants, higher levels of GPx and CER, and lower levels of the marker of oxidative damage, MDA, in comparison with the control group (Table 3). In fact, as far as antioxidant enzymes are concerned, studies of hypertensives have found low levels of SOD, CAT and GPx[17-19] (Table 3) similarly to those of this study, except GPx, which was inexplicably high for Ide et al[20].

Catalase may be inhibited in the presence of inadequately removed $O_2^{\bullet-}$, generating ferroxycatalase which does not decompose H_2O_2 rapidly[10]. This would explain not only the low CAT levels but also the high GPx levels, possibly indicating a greater demand for this enzyme, since it is able to reduce $ONOO^-$ efficiently, thus preventing macromolecular oxidation and protein nitration[10]. Moreover, although no significant differences were found in SOD, one can consider that the reduced levels of this enzyme were probably due to the reaction of $O_2^{\bullet-}$ and $^{\bullet}NO$, which is faster than the reaction of $O_2^{\bullet-}$ and SOD, along with the fact that it acts more efficiently in physiological conditions (low concentration of $O_2^{\bullet-}$). Returning to CAT, one can consider that, with $O_2^{\bullet-}$ "deviated" to form $ONOO^-$, H_2O_2 production via SOD is lower or remains at normal levels, not requiring extra activity. Moreover, as mentioned earlier, this enzyme can be inhibited in the presence of accumulated $O_2^{\bullet-}$ and its action confined to the cell's peroxisomes.

Concerning drug therapy, the antihypertensive medications that act as antioxidants are: (1) ACE inhibitors and AT_1 receptor blockers, which act indirectly by inhibiting the renin-angiotensin-aldosterone system (RAAS), an important source of ROS in the endothelium [3,4,7,8,11]; (2) third generation beta-blockers, by increasing the release of $^{\bullet}NO$ and glutathione in the endothelial cell[21]; and (3) calcium channel blockers, by

Table 4 - Studies of biomarkers of oxidative stress in hypertension

Studies/ References	n	Biomarkers Studied	Results Obtained H *vs.* C[a] and H[b]
19	H = 30 C = 164	SOD and GPx	SOD and GPx decreased[a]
34	H = 30 C = 30	F_2ISO	No difference[a]
18	H = 66 C = 16	GSH, GSSG, GSH/GSSG SOD, CAT, GPx, MDA, 8-OxoGUA	GSH/GSSG and MDA augmented[a] SOD, CAT, GPx and GSH decreased[a]
34	H = 38 C1 = 21 C2 = 17	GSH SOD, CAT, GPx, GST Nitrate/Nitrite Carbonyl and MDA	Carbonyl and MDA augmented[a] SOD decreased[a] CAT and GPx similar[a]
24	H = 89	GSH, GSSG,GSH/GSSG SOD and MDA	AO raised and MDA [b] decreased
23	H1 = 70 H2 = 85 C = 40	F_2ISO Vitamin C and E, Uric Acid	F_2ISO decreased in H treated (H2)[a]
17	H and C, do not refer to n	GST, GPx. Asc., thiols FRAP (Fe 3+)	GST, GPx, Asc., Thiols and FRAP decreased[a]
37	H + ICC = 23 C = 50	SOD and CAT MDA	SOD and CAT augmented[a] MDA decreased[a]
20	H = 39	FRAP	FRAP raised H diuretic[b]
36	H = 83 C = 50	F_2ISO CRP and TNFα	F_2ISO augmented[a] CRP and TNFα augmented[a]

H – Hypertensive; C – Control; SOD - superoxide dismutase; GPx - glutathione peroxidase; F2ISO- F2-Isoprostane; GSH - glutathione reduced form; GSSG - glutathione oxidized form; MDA – malondialdehyde; CAT – catalase; 8-OxoGUA - 8-oxoguanina; GST - glutathione S-transferase; AO – antioxidant; Asc – Ascorbate; FRAP - Ferric reducing ability of plasma; CRP- C reactive protein; TNFα -Tumor necrosis factor-alpha.

increasing the availability of nitric oxide in the endothelial cell and increasing the expression of MnSOD in vascular smooth muscle cells[22].

In the hypertensive group, the use of an ACE inhibitor (captopril) by 60% of the patients (40% with 25 mg/day and 20% with 50 mg/day) requires additional comments. The antioxidant mechanism of this medication, though indirect and without a defined dose-response relationship, involves inhibition of the RAAS by inhibiting the action of angiotensin II (ANG II), which is the antioxidant link and a potent stimulus for ROS production in the endothelial cell, increasing the NADPH oxidase activity. In addition, ANG II also supra-regulates eNOS activity, which is accompanied by decoupling of the enzyme, reduction of •NO production and increase of superoxide production[10]. This effect was observed in a study that found an inverse association between f2-isoprostane and number and type of antihypertensive medication: 46% of treated hypertensive patients were using ACE inhibitor and 26%, AT1 receptor blocker[23]. In addition, the antioxidant action of beta-blockers and AT_1 receptor antagonists was also reported in a study of hypertensives treated with these drugs, whose SOD, CAT and GPx levels increased and 8-oxo-2'-deoxyguanosine and MDA levels decreased[24]. In contrast, another study[25] found increased total antioxidant capacity in the plasma of hypertensives using thiazide diuretic, but did not find the same positive correlation with ACE inhibitor and beta-blocker, despite their antioxidant action.

The positive correlation evidenced between SBP and MDA in hypertensives is indicative of the association between HAS and oxidative stress, mainly after the negative relationship obtained between MDA and GPx in both groups.

Because glutathione acts together with GPx, the results were analyzed jointly, considering both of them fundamental in the defense against lipid peroxidation. Each unit of GPx acts by consuming 2 molecules of GSH, which is the most important intracellular antioxidant and is present in the cell predominantly in the reduced form (GSH), to the detriment of the oxidized form (GSSG). The GSH/GSSG > 1 ratio, which is vital for the cell, is maintained by an efficient recycling system of GSH from GSSG[10].

In hypertension, low GSH levels and GSH/GSSG <1 ratio have both been found[18]. In this study, GSSG was not measured. Our findings of low GSH levels are consistent with the literature and would be explained by oxidative stress, since ROS oxidize GSH to GSSG, leading to a drop in GSH, which is worsened by the conversion of GSH into GSSG in the process of peroxide detoxification by the action of GPx.

As for uric acid and vitamin C, the higher levels observed in the hypertensive group were not statistically different, although it is known that hyperuricemia is associated with hypertension[28] and the antioxidant activity of urate involves different reactions (with $R^{\bullet}$, $ROO^{\bullet}$, $ONOO^{-}$, and $ONO_2^{\bullet}$)[10,14] acting cyclically, since it can be recovered by ascorbate, among others. It is considered a potent plasmatic antioxidant, once its concentration in plasma is tenfold higher than other antioxidants such as vitamins E and C[13].

The transferrin levels were similar in the two groups, but the levels of ceruloplasmin, which is also a ferroxidase, were higher in the hypertensive group (Table 3). This finding also represents an important factor of protection, in view of the activity of ceruloplasmin in transporting copper and oxidizing iron for capture by transferrin, i.e., it acts on the most important transition metals with respect to the ability to transfer electrons in their free form in biological systems. Other antioxidant mechanisms include $O_2^{\bullet-}$ and H_2O_2 sequestration, inhibition of the Fenton reaction, protecting the biological tissues from the damaging effects of iron decompartmentalization, inhibition of lipid oxidation and blocking of protein and DNA damages, which is verified by inhibition of carbonyl formation and protection of the cell against damage and lysis caused by ROS[11,27]. However, under oxidative stress, ceruloplasmin may act as a prooxidant in the intravascular medium, since $ONOO^{-}$ and H_2O_2 can induce the dissociation of the free Cu^{2+} bond of the protein, favoring its release into the intracellular medium, as well as diminishing its ferroxydase activity[27]. Indeed, several studies have found a correlation between ceruloplasmin and cardiovascular disease, and some prospective studies and control cases have indicated it as a cardiovascular risk factor[28]. This is a biomarker whose prooxidant activity seems to predominate in certain circumstances, including cardiovascular disease.

A decrease was observed in the phenomenon of lipid peroxidation (LP) among the hypertensives, since the presence of MDA (the most abundant reactive aldehyde of LP) in the serum of these individuals was lower than in that of the controls (Table 3). The presence of carbonyl groups at similar levels, in this case, may reinforce the assumption that, if the hypertensive group was under oxidative stress, $ONOO^{-}$ would be the prevailing reactive species, since it is a poor inducer of carbonyl proteins[37]. It is worth mentioning that, in the choice of the marker of oxidative stress, the nature of the oxidative stress under study plays an extremely important role. However, the methodology available and the feasibility of applying analytical techniques are of equal importance, and were particularly determinant in the choices for this study.

Several studies have found a positive correlation between high levels of MDA and cardiovascular diseases such as acute myocardial infarction, congestive heart failure and hypertension[29-31] in hypertensives without drug therapy[18] and in elderly hypertensives using antihypertensive medication[32]. On the other hand, studies involving hypertensives who have never been treated[33] and treated hypertensives[23,34] found no differences, among hypertensives and controls, in the levels of F_2-isoprostane, another marker of lipid peroxidation, despite the antioxidant action of antihypertensive drugs. However, another study found a positive correlation between this damage marker and inflammation markers in hypertensives not yet under drug therapy[35]. Patients with class II to class IV congestive heart failure showed reduced levels of MDA[36]. The results indicate the possible association and LP protection mechanisms, such as GPx and CER, which were found in high levels.

It is worth pointing out that, in the study population, an existing bias was the use of medication. However, antihypertensive drug therapy (especially calcium channel-

blocking drugs and ECA inhibitors) produces a significant increase of •NO, but antioxidant enzyme levels remain low when compared with normotensives[17]. Another interesting aspect is the possibility of CER inhibiting protein oxidation, which was found in an endothelial cell culture through the formation of carbonyl in the presence of ceruloplasmin[38].

The phenomenon of oxidative stress, as well as the antioxidant system, works in an integrated fashion, in a series of related events. This characteristic and the complexity of these processes necessarily require a non-compartmentalized discussion. Moreover, one must keep in mind the duality of the redox environment: high antioxidant levels are not necessarily desirable or low antioxidant levels undesirable since both may result in oxidative stress.

Although it is not clear whether oxidative stress in hypertension is a cause or an effect, the occurrence of oxidative stress in hypertension was found in this study, corroborating previously published findings.

The role of oxidative stress in hypertension is already clear and well founded. However, although various studies point to endothelial dysfunction and to the imbalance between the reactive oxygen and nitrogen species and antioxidant defenses, it is not possible to define whether redox imbalance is a cause or a consequence of blood pressure homeostasis. This study revealed oxidative stress in hypertension. Nevertheless, additional studies are needed to elucidate the mechanisms that lead to the genesis of this and other clinical situations characterized by endothelial dysfunction involving redox imbalance. Hence, our research group is currently engaged in studies based on biomarkers of redox imbalance in patients with metabolic syndrome, refractory hypertension and diabetes mellitus, which, like hypertension, are diseases whose common denominator is the endothelial dysfunction.

Conclusion

Lastly, it can be concluded that, with regard to antioxidants and oxidative damage markers, the reduced CAT and GSH levels and high ceruloplasmin levels found in the hypertensive patients indicate that they are under oxidative stress, despite the possible mitigating effect of their antihypertensive medication. High GPx and low MDA levels may also result from oxidative stress, since (1) the enzyme would be in greater demand in the presence of excess $ONOO^-$, a reactive species characteristic of hypertension, and (2) due to its significant action upon $ROO^•$, there would be a decrease in LP, with a consequent reduction of MDA. Hence, the oxidative stress of hypertension, as far as these biomarkers are concerned, would be explained by an alternative mechanism.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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