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A CASE CONTROL STUDY OF OXIDATIVE STRESS AND INFLAMMATION IN TUNISIAN PATIENTS WITH ISCHEMIC HEART DISEASE

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ABSTRACT: Ischemic heart disease (IHD) is the major cause of morbid-mortality in most countries. The involvement of inflammation and oxidative stress (OS) in the development of atherosclerosis, ischemic cardiopathy triggering phenomenon, has been investigated. The high sensitive C-reactive protein (hs_CRP) was measured in serum by immunoenzymatic method. Serum total homocysteine (Hcy) concentration was measured by fluorescence polarization immunoassay. Plasma levels of substances reacting with thiobarbituric acid (TBARS) were carried out by fluorimetric method (Yagi). Erythrocyte activity of superoxide dismutase (SOD) and plasma total antioxidant status (TAS) were determined by a colorimetric method at 505nm and 600nm, respectively. Erythrocyte activity of catalase (CAT) was measured by colorimetric assay (Goth). Our study showed significant elevation of hs_CRP, TBARS and Hcy levels in patients compared to controls. While we noted significant decrease in TAS levels, SOD and CAT activities in patients compared to the control group. We also noted positive correlations between: hs_CRP-Hcy, hs_CRP-TBARS, Hcy-TBARS, SOD-TAS, CAT-TAS and negative correlations between: hs_CRP-SOD, hs_CRP-CAT, hs_CRP-TAS, TBARS-SOD, TBARS-CAT, TBARS-TAS, Hcy-SOD, Hcy-CAT and Hcy-TAS. This unsuitability, elevated pro-oxidant rate parameters (Hcy and TBARS) and decrease of antioxidant parameters (SOD, CAT and TAS), is a consequence of inflammation, one of the mechanisms which cause atherogenesis. So our study supports the hypothesis involvement of inflammation and OS in the genesis and progression of atherosclerosis.

INTRODUCTION: Inappropriate oxidation of biomolecules is a hazard associated with all aerobic life. Harmful oxidation is often mediated by reactive oxygen species (ROS) that were generated by a wide range of biological processes, including mitochondrial respiration and both enzymatic and non-enzymatic chemical reactions ¹.

The fine balance between ROS and antioxidants - that "neutralize" ROS before they are able to react with cellular components and alter their structure or function- ² is disturbed when excessive amounts of free radicals (FR) are produced or antioxidant capacity is decreased ³.

Antioxidants are substances endogenous and substances derived from diet; Endogenous antioxidants include superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), GSH peroxidase (GPx), thioreductase, and uric acid. Dietary sources include Vitamins A, C, and E ¹. The total antioxidant status (TAS) mirrors the activity potential of the antioxidant system because

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antioxidative effects of the plasma antioxidant components are additive⁴.

Pro-oxidant substances can be described as either FR species or non-radical species that mediate peroxidation; the two major sub-groups are ROS and reactive nitrogen species (RNS)¹. This disturbance known as oxidative stress (OS) plays an important role in cardiac pathophysiology³ which is one of the major health problems of developing countries of the world⁵.

Ischemic heart disease (IHD) results from the interaction between two primary mechanisms: atherosclerosis and thrombosis⁶.

Currently, an increasing number of studies suggest that levels of OS markers in body fluids correlate with atherosclerotic disease activity³ and it's a critical key in most steps of the atherogenesis⁷.

Inflammation is a cause of several human disease⁸ especially diseases including initiation and progression of atherosclerotic plaque, plaque rupture, and thrombosis (atherothrombosis)⁷.

One of the most important inflammatory biomarkers is high sensitive C-reactive protein (hs_CRP) which synthesized by hepatocytes in response to pro-inflammatory cytokines in particular interleukin-6⁹.

It is very important to recognize that the analyte designated as hs_CRP is just CRP itself. In fact, hs_CRP is then same exquisitely sensitive and entirely nonspecific systemic marker of infection, inflammation, tissue damage and/or almost any form of adverse non-physiological stress as the CRP, which has been extensively studied and used clinically¹⁰.

The hyperhomocysteinemia is another factor that acts either independently of atherosclerosis and thrombosis^{6, 10} or by increase thrombosis¹¹. Several studies support the hypothesis that inflammation, hyperhomocysteinemia and OS were intimately linked with the pathogenesis of oxidative myocardial damage with consequential IHD^{12, 13, 14}.

Our study attempted to assess inflammation, hyperhomocysteinemia and OS in atherosclerosis and its contribution to the IHD. This was accomplished by evaluation of levels and correlations between hs_CRP, Hcy, TBARS, SOD, CAT and TAS.

MATERIALS & METHODS:

Study population: The present study had involved 268 patients (mean-age: 61 ± 12 years) recruited, from the Cardiology Department of the University Hospital, Farhat Hached, Sousse-Tunisia. All cases fulfilled these inclusion criteria: presenting symptoms and signs suggestive of IHD such as chest pain and dyspnea supported by electrocardiogram (ECG) and cardiac markers. Patients having revascularization, Infection, cerebrovascular accident (CVA), transplantation, liver disease, renal failure, Cancer, splenomegaly, intermittent claudication and those with other major illness were excluded from the study.

The control group consisted of 176 healthy volunteer subjects (mean-age: 46 ± 7 years). All patients and controls gave informed consent to participate in this study which was approved by the National Medical and research Ethics Committee. The methods carried out in the study are in accordance with the approved relevant guidelines and regulations.

Blood samples processing:

Venous blood samples from patients and healthy volunteers were collected in fluoride, heparinized and without anti-coagulant tubes. Plasma glucose levels, renal profile (urea, creatinin, uric acid) levels and serum total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (C_HDL) were measured with colorimetric assay using an automated system (Cx5 and Cx9 Pro-Bechman Coulter-Fuller-Ton CA). Low density lipoprotein cholesterol (C_LDL) was calculated using Friedwald's formula: $C_LDL = (C_HDL + TG/2.2)^{15}$.

Serum was used to determine hs_CRP according to the instructions of the manufacture using microparticulate immunoenzymatic method (COBAS-INTEGRA 400, Roche) and Hcy levels

by fluorescence polarization immunoassay (FPIA) from AxYM Abbott diagnostics. Lipid peroxidation was estimated by the determination of plasma TBARS levels according to the fluorimetric method of Yagi ¹⁶. The heparinized whole blood was used to determine the erythrocyte activities of SOD by a colorimetric method at 505 nm (RANDOX Kits) in Daytona – analyser. Erythrocyte CAT activity was measured using the molybdate colorimetric method described by Góth et al.1991 ¹⁷. SOD and CAT activities were expressed in kilo unit per gram of hemoglobin (Hb). Hb was determined using spectrophotometric method of David L. Drabkin 1932 ¹⁸ by (Beckman coulter LH750) Analyser. TAS levels were determined in plasma by colorimetric method at 600 nm according to the method of Miller et al ¹⁹ (RANDOX Kits) in Daytona – analyser.

Statistical Analysis: Data base management and statistical analyses were performed by the SPSS

(Statistical Package for the Sociological Sciences) software, version 17.

When the data presented a Gaussian distribution, parametric tests were used (student’s test for differentiating averages and Pearson’s correlation coefficient for determination of relationships between parameters). When the data did not have a Gaussian distribution, non-parametric tests were used (the Wilconxon’s test for differentiating averages and Spearman’s correlation coefficient for determination of relationships between parameters). P values less than 0.05 were considered as significant.

RESULTS: Anthropometric characteristics of the study groups are presented in **Table 1**. The mean age’s ±SD of the IHD patients and controls was significantly different. However, the body mass index (BMI) was significantly higher in subjects compared to the controls.

TABLE 1: RISK FACTOR DISTRIBUTION IN THE POPULATION.

Risk factors		Patients (N=268)	Controls (N= 176)
Sex	Age (x± SD, years)	62±12	46±7
	Mean (%)	68.5	43.18
	Women (%)	31.5	56.82
	BMI (x± SD, kg/m ²)	24.93±5.40	23±2.17
	Diabetes (%)	44.1	0
	Hypertension (%)	48.6	0
	smoking (%)	61.5	0
	Alcohol (%)	3.5	0
	Dyslipidemia (%)	27.6	0

N: number of subjects, x: mean, SD: Standard Deviation, BMI: Body Mass Index

The comparison of biochemical parameter variations between IHD cases and controls are shown in **Table 2**. Patients had significantly higher glucose, urea, creatinin, uric acid, CT, TG and

C_LDL levels than the control group, while no significant differences observed on C_HDL levels between patients and healthy subjects.

TABLE 2: BIOLOGICAL PARAMETER VARIATIONS IN PATIENTS AND CONTROLS.

Parameters	Patients (N=268) x±SD	Controls (N= 176) x±SD	p
Glucose (mmol/l)	8.29± 4 .54	4.94±0.70	<10 ⁻³
Urea (mmol/l)	8.21±5.17	4.85±1.39	<10 ⁻³
Creatinin (µmol/l)	115.68±78.61	72.94±23.98	<10 ⁻³
Uric acid (µmol/l)	372.89±171.77	219.34±87.26	<10 ⁻³
CT (mmol/l)	4.58± 1.21	4.28±0.95	0.05
TG (mmol/l)	1.66± 0.95	1.20±0.66	<10 ⁻³
C_HDL (mmol/l)	1.24± 0.59	1.28±0.41	NS
C_LDL (mmol/l)	5± 0.88	2.43±0.75	<10 ⁻³

N: number of subjects, x: mean, SD: Standard Deviation, p: significance (2-tailed), CT: cholesterol, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein.

Our result reveled significant elevation in interquartile range of hs_CRP. Hcy and TBARS rates were elevated in patients compared to controls. While we noted significant decrease in

TAS levels, SOD and CAT activities in patients compared to the control group (**Table 3**).

TABLE 3: INFLAMMATORY AND OXIDATIVE STRESS PARAMETER VARIATIONS IN PATIENTS COMPARED TO CONTROLS.

Parameters	Patients (N=268)	Controls (N= 176)	p
hs_CRP (mg/l, IQR)	20.45 [14.82; 22.2]	1.42 [0.6; 2.57]	<10 ⁻³
Homocystein (x±SD, µmol/l)	24.02±9	11.37±4.53	<10 ⁻³
TBARS (x±SD, µmo/l)	1.82± 0.72	0.65± 0.35	<10 ⁻³
SOD (x±SD, U/g Hb)	1182±576	1621±627	0.03
CAT (x±SD, U/g Hb)	280.54 ± 159.34	364.67 ± 92.84	<10 ⁻³
TAS (x±SD, mmol/l)	1.59±0.49	1.75±0.22	<10 ⁻³

N: number of subjects, IQR: inter-quartil range, x: mean, SD: Standard Deviation, p: significance (2-tailed), hs_CRP: high sensitive C-reactive protein, TBARS: Substances reacting with thiobarbituric acid, SOD: superoxide dismutase, CAT: catalase, TAS: Total antioxidant status.

Our study showed significant positive correlations between: hs_CRP-Hcy ($r= 0.73, p <10^{-3}$), hs_CRP-TBARS ($r= 0.76, p <10^{-3}$), Hcy-TBARS ($r= 0.78, p <10^{-3}$), SOD-TAS ($r= 0.71, p <10^{-3}$), SOD-CAT ($r= 0.788, p <10^{-3}$) and CAT-TAS ($r= 0.75, p <10^{-3}$) (Fig 1).

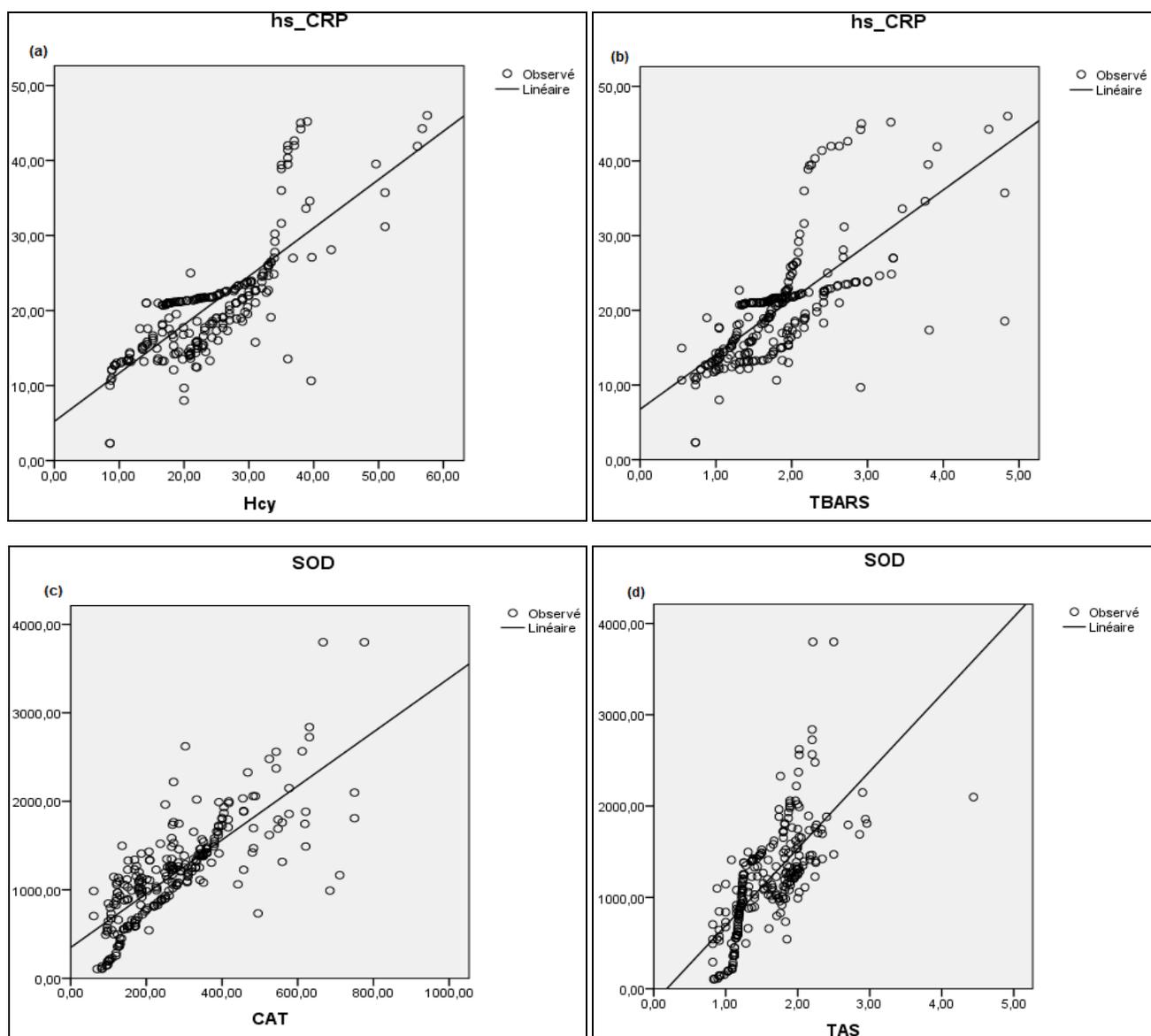


FIG. 1: POSITIVE CORRELATIONS AMONG IHD PATIENTS (hs_CRP-Hcy, hs_CRP-TBARS and SOD-TAS).

Fig. 1 legend: Positive correlations among IHD patients (hs_CRP-Hcy, hs_CRP-TBARS, SOD-TAS and SOD-CAT): “It is a bottom line that represents the relationship between; (a): hs_CRP (mg/l) and Hcy ($\mu\text{mol/l}$) rates, (b): hs_CRP (mg/l) and TBARS ($\mu\text{mol/l}$) rates, (c): SOD and CAT activities (U/g Hb), (d): SOD activity (U/g Hb) and TAS level (mmol/l). hs_CRP: high sensitive C-reactive protein, Hcy: homocysteine, TBARS: substances reacting with thiobarbituric acid, SOD:

superoxide dismutase, CAT: catalase, TAS: Total antioxidant status”. However significant negative correlations between hs_CRP-SOD ($r=-0.79, p<10^{-3}$), hs_CRP-CAT ($r=-0.65, p<10^{-3}$), hs_CRP-TAS ($r=-0.83, p<10^{-3}$), TBARS-SOD ($r=-0.71, p<10^{-3}$), TBARS-CAT ($r=-0.59, p<10^{-3}$), TBARS-TAS Hcy-SOD ($r=-0.66, p<10^{-3}$), Hcy-CAT ($r=-0.67, p<10^{-3}$), and Hcy-TAS ($r=-0.49, p<10^{-3}$) were observed (**Fig. 2**).

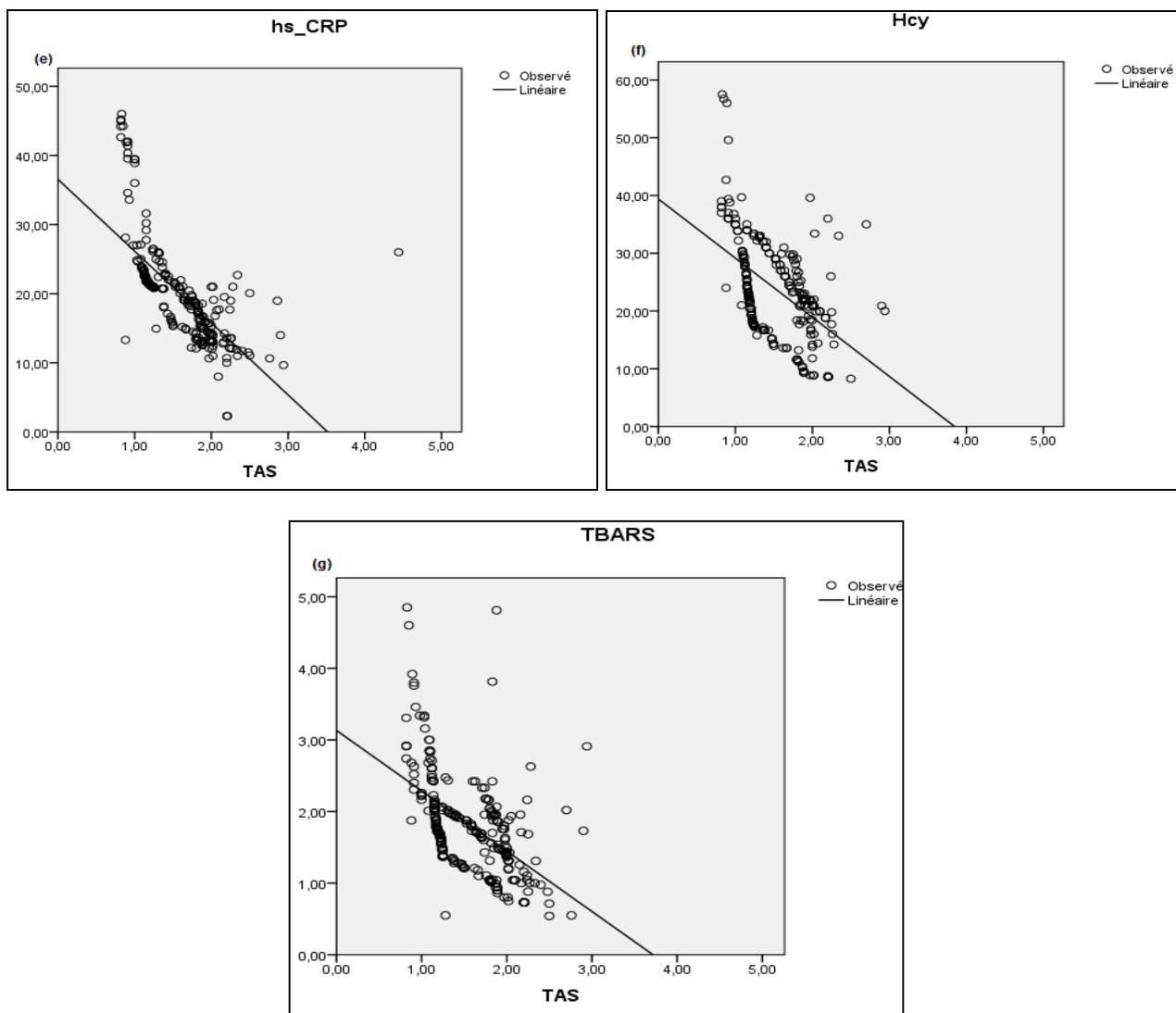


FIG. 2: NEGATIVE CORRELATIONS AMONG IHD PATIENTS (hs_CRP-TAS, Hcy-TAS and TBARS-TAS).

Fig. 2 Legend: Negative correlations among IHD patients (hs_CRP-TAS, Hcy-TAS and TBARS-TAS): “It is a bottom line that represents the relationship between; (e): hs_CRP (mg/l) and TAS (mmol/l) rates, (f): Hcy ($\mu\text{mol/l}$) and TAS (mmol/l) rates, (g): TBARS ($\mu\text{mol/l}$) and TAS level (mmol/l), hs_CRP: high sensitive C-reactive protein, TAS: Total antioxidant status, Hcy:

homocysteine, TBARS: substances reacting with thiobarbituric acid”.

DISCUSSION: IHD patients in this study showed a significant increase in serum hs_CRP levels, which is consistent with the findings observed by other investigators²⁰.

In healthy young adult volunteer blood donors, the median concentration of CRP is 1.42 mg/l and the 75th centile is 2.57mg/l, but, following an acute-phase stimulus, values may increase to 0.6 mg/l.

Elevated hs-CRP level was detectable during significant inflammation in most patients which is associated with an increase risk of IHD⁹. Hypertension, diabetes mellitus, older age, hyperlipidemia seems to be responsible for the elevation of hs-CRP levels^{21, 22}.

CRP may be involved in all phases of atherosclerosis, from the initial recruitment of circulating leukocytes to the arterial wall to the rupture of unstable plaques, which results in the clinical manifestations of the disease.

Furthermore, Oxygen free radicals (OFR): superoxide anions (O⁻) and hydroxyl radicals (OH⁻), produced by reduction of oxygen, have been implicated in cardiac ischemic injury.

In normal circumstances they are removed by the different scavenger systems presents in blood and tissues. In case of myocardial ischemia which can lead to myocardial infarction, unstable angina and heart failure, excessive ORF may be generated²³.

Our findings show a significant increase in plasma TBARS levels. This is in accordance with those of Khaki-khatibi F et al., high TBARS levels might be resulted from increase lipid peroxidation that's marker of OS^{22, 24}.

Lipid peroxidation may increase endothelial permeability of triglycerides which causes increase blood viscosity and possibly through oxidative damage of erythrocytes. Lipid peroxidation may also promote acute-phase reactions by increasing endothelial/monocyte interactions and release cytokines, which are mediator's key of inflammatory reactions resulting elevation of CRP^{25, 26}.

Increased serum Hcy levels in IHD patients compared to controls is in close conformity with other findings¹⁴ witch indicate that elevated Hcy was an independent risk factor (RF) for atherosclerotic disease in coronary, cerebral and

peripheral arteries and show a correlation between hyperhomocysteinaemia and several atherosclerosis RF (hypertension, diabetes, smoking, dislipidemia^{14, 27}).

Other studies support the hypothesis that Hcy is a pro-oxidant marker. In fact, the sulfhydryl groups in Hcy were oxidized to disulfide, catalyzed by the transition metals which product several OFR (hydroperoxides: H₂O₂), and initiates lipid peroxidation responsible of endothelial injury^{11, 28}.

Erythrocyte SOD activity was significantly decreased in IHD cases wich is in agreement with several studies such as those reported by Almzaiel AJT et al.^{14, 29, 30}. SOD, FR scavenging enzyme, are the first line of cellular defense against oxidative injury²⁰. SOD is responsible for converting superoxide radical to H₂O₂⁵ before interacting to form more reactive hydroxyl radical (SOH). This enzyme protects the red cells against O⁻ and OH⁻ mediated lipid peroxidation. Decrease in the activity of SOD could be due to inactivation of the enzyme by cross linking or due to exhaustion of the enzymes by increased peroxidation²⁰.

Thus, low level of SOD activity could reflect either a possible accumulation of H₂O₂ which has the potential to bring about oxidative tissue damage, or low capacity of defense against it. High OS status has been reported in IHD patients, even in stable cases²³.

We have also observed a significant decrease in the activity of CAT in patients with IHD, as compared to controls. CAT, enzyme that catalyse the conversion of H₂O₂ to H₂O and O₂ using either an iron or manganese cofactor³¹, is inactivated when counteracting these FR³².

Moreover, treatment with antioxidant enzymes; SOD plus CAT, can protect the heart against these changes^{33, 34, 35}.

Present study revealed a significant decrease in the levels of TAS. These results are in agreement with those reported by Khaki-khatibi F et al.²².

One possible explanation of these findings is depletion of the antioxidant barrier as an effect of long term OS^{30, 36}.

This study has some limitations which have to be pointed out. Our study did not compare results of other enzymatic/non enzymatic antioxidant (peroxidase glutathione, reductase glutathione, ceruloplasmin and transferin). We did not assess the protein peroxidation by measuring carbonyl proteins to show another pro-oxidant effect. However, this will be the subject of ongoing studies.

CONCLUSION: Our study supports the hypothesis that the generation of ROS and induction of inflammation are intimately linked with the initiation and progression of atherosclerotic plaque which can lead to myocardial infarction, Unstable Angina or heart failure.

CONFLICT OF INTERESTS: The authors declare that they have no competing interests.

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