Impact of Lipid Profile, Cardiac Biomarkers, Serum Angiotensin-Converting Enzyme Activity, Oxidative Stress and Antioxidant on Blood Pressure Status

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Research Article

Keywords: Blood pressure, non-ST-elevated myocardial infarction, Heart rate product, antioxidant status, serum ACE activity, oxidative stress, cardiac biomarkers.

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Abstract

The hemodynamic determinants of myocardial oxygen demand measured were heart rate (HR), systolic blood pressure (BP), and rate pressure product (RPP). This study aimed to evaluate the impact of lipid profile, cardiac biomarkers, and serum angiotensin-converting enzyme (ACE) activity, oxidative stress (plasma malondialdehyde, MDA; conjugated diene, DC), and antioxidant status (glutathione peroxidase, GPx) on BP. Three hundred and six non-ST-elevated myocardial infarction (NSTEMI) patients compared to 410 healthy controls. The diastolic and systolic BP was correlated positively with serum ACE activity. The rate pressure product (RPP) was correlated negatively with Fasting glucose (r= -0.144; p = 0.012), HbA1c (r= -0.117; p = 0.041) and GPx activity (r= -0.148; p = 0.009), and positively with smoking (r = 0,197; p = 0.001), BMI (r = 0,219; p = 0.001), peak cTnI (r = 0.131; p = 0.022), serum ACE activity (r = 0,190; p = 0.001) and DC level (r = 0.189; p = 0.001) in NSTEMI patients. Regarding healthy controls, no correlation was found between the diastolic or systolic BP with serum ACE activity, peak cTnI, MDA, DC level, GPx activity, and lipid parameters. The existence of a specific correlation between the rate pressure product, diastolic and systolic BP and, lipid profile, serum ACE activity and, cardiac biomarkers, oxidative stress, and antioxidant status increase the NSTEMI risk on patients.

Introduction

Acute myocardial infarction (AMI) is a term that is used for defining the necrosis in the heart muscle due to the lack of the oxygen need of myocardium which cannot be supplied by the coronaries. Some disease factors contribute to increasing the risk of acute myocardial infarction (AMI) such as diabetes mellitus, hypertension (HTA), high blood pressure (BP), hypercholesterolemia, and obesity[1–3]. Endothelial dysfunction is a central initiating factor of the increased atherosclerosis which has been associated with an increased risk of AMI in diabetics patients[4]. Diabetes is associated with a 2 to 4 fold increase of the risk for AMI [5]. HbA1c levels of more than 7% are associated with a significant increase in the risk of cardiac events and deaths [6]. In diabetics patients, the incidence and severity of microvascular disease are directly related to the duration and severity of hyperglycemia, and macrovascular disease is related to insulin resistance and hyperinsulinemia with diffuse vessel involvement [7].

HTA is an important risk factor for AMI [3]. The frequency of HTA increases with age. Individuals with high BP may have a six-fold greater risk of MI [8]. Many guidelines recommend a target BP of more than 140/90mmHg to increase cardiovascular outcomes[9]. The Systolic BP is the most important determinant of AMI [10]. The hemodynamic determinants of myocardial oxygen demand measured were heart rate (HR), systolic BP, and rate pressure product (RPP). HR is a major determinant of myocardial oxygen consumption and energy utilization [11]. Oxygen (O_2) is widely used in people with AMI. Moreover, oxidative stress is reported to be an efficient mechanism for the generation of oxidized low-density lipoprotein and subsequently atherosclerosis [12]. Prooxidative processes produce some molecules which may indicate the intensity of oxidative stress. In patients with AMI, the underlying mechanism in the increase of mortality associated with blood pressure is poorly understood.

Myocardial cell protection and prevention of cell ischemia/necrosis have been therapeutic targets for a long time. Moreover, lifestyle changes and therapeutics that may reduce adiposity could offer the benefit of preventing AMI related morbidity and mortality. The present study aimed to evaluate the impact of correlation the high blood pressure on the NSTEMI patients with all the parameters studied such as lipid profile, cardiac biomarkers, and serum angiotensin-converting enzyme (ACE) activity, oxidative stress (plasma malondialdheyde, MDA; conjugated diene (DC) and antioxidant status (glutathione peroxidase, GPx).

Material And Methods

Study Design

The study was carried out on 306 unrelated patients and affected with non-ST-elevated myocardial infarction (NSTEMI) originated from the governorate of Tunis were recruited from the department of cardiology of Rabta Hospital. AMI was defined according to the World Health Organization criteria. A diagnosis of NSTEMI was accepted in the absence of ST-segment elevation, the presence of ischemic ST-segment or T-wave changes for 24 h with positive cardiac enzymes, and/or atypical clinical presentation. Cardiac catheterization and coronary angiography were performed according to the standard procedures. All patients were admitted with the acute coronary syndrome and underwent coronary angiography.

Patients who suffered from stable or unstable angina instead of myocardial infarction, congenital heart diseases, valvular heart diseases, cardiomyopathy, viral myocarditis, sarcoidosis, or severe arrhythmias were excluded from the study. Cardiovascular risk factors and current treatment were obtained from each patient using a standard questionnaire. This study was approved by our hospital ethical committee, and informed consent was obtained from all healthy controls and patients before their enrolment.

Four hundred and ten healthy persons matched for sex, age, and geographic origin were enrolled as healthy controls in the study. They came from a population of genetically unrelated friends of the patients. Family history, cardiovascular risk factors, and current treatment were obtained from each patient using a standard questionnaire. The body mass index (BMI) was calculated as weight divided by height^2. The body mass index (BMI) was calculated as weight divided by height^2. Hypertension was defined as the presence of elevated systolic ≥ 140mmHg and/or diastolic ≥ 90 mmHg blood pressure and/or the current use of antihypertensive drugs. Diabetes was defined as if they had a fasting blood glucose level ≥ of 7.0 mmol/l or being treated for diabetes.

Rate pressure product (RPP), which can be used to estimate the increased metabolic demand that exercise places on the heart, is calculated by multiplying the HR and the SBP.

Biochemical Measurements

Biochemical measurements were carried out according to validated methods. Plasma glucose concentration was evaluated using an enzymatic kit (glucose oxidase, Randox, Antrim, UK), total cholesterol and triglycerides by enzymatic methods using Randox reagents and LDL and HDL cholesterol determined as described by Smaoui et al.[13] Serum ACE activity and troponin I (cTn-I) were determined as described previously[3, 14].

Lipid peroxidation was determined by measuring the production of malondialdehyde (MDA) in the plasma following the method of Yoshioka et al. [15] Conjugated diene (CD) (a marker of the lipid peroxidation) were measured as described by Esterbauer et al. [16] GPx activity was measured according to Flohe and Günzler. [17]

Statistical Analysis

Continuous variables according to a Gaussian distribution were expressed as mean and standard deviation (mean ± SD) and compared using a one-way-ANOVA. A value of $p < 0.05$ was considered statistically significant. Correlation analysis was performed using the Pearson rank order test. All statistics were carried out using Software Package for Social Sciences (SPSS) version 11.0 (SPSS, Chicago, IL, USA).

Results

A total of 306 NSTEMI patients and 410 healthy controls were included in the study. The mean age of NSTEMI patients was 63.5 ± 11.72 years. Baseline clinical characteristics of the study patients are shown in Table 1. BMI, fasting glucose, triglycerides, total cholesterol, LDL, and HDL cholesterol showed higher statistical significance between NSTEMI patients and healthy controls ($P < 0.001$). All NSTEMI patients are hypertensive and diabetic. The heart rate (HR) (was significantly higher in patients compared to controls ($p = 0.013$).

Table 1
The characteristics of NSTEMI Patients and healthy controls

	NNSTEMI Patients (n = 306)	Healthy Controls (n = 410)	P
Mean age (years)	63.5 ± 11.72	62.12 ± 9.75	0.085
Sex (male/female)	163/143	228/182	0.292
Smoking, n (%)	220(71.9)	75(18.3)	< 0.001
BMI (kg/m^2)	29.01 ± 6.07	26.84 ± 4.21	< 0.001
Fasting glucose (mmol/L)	6.08 ± 1.45	4.75 ± 1.28	< 0.001
Total cholesterol (mmol/L)	8.81 ± 1.84	4.18 ± 0.94	< 0.001
LDL-C (mmol/L)	6.17 ± 1.50	2.26 ± 0.24	< 0.001
HDL-C (mmol/L)	1.95 ± 0.23	1.10 ± 0.21	< 0.001
Triglycerides(mmol/L)	2.28 ± 0.93	1.32 ± 0.59	< 0.001
HbA1c(%)	9.2 ± 1.65	4.6 ± 0.75	< 0.001
SBP (mm Hg)	158.76 ± 23.64	128.06 ± 7.64	< 0.001
DBP(mm Hg)	97.38 ± 15.50	81.6 ± 6.10	< 0.001
HR(bpm)	78.9 ± 15.5	76.7 ± 5.2	0.013
RPP(mm Hg. Bpm)	12488.2 ± 3062.2	9830.4 ± 918.4	< 0.001
Serum ACE activity (U/L)	96.85 ± 34.30	87.35 ± 27.40	< 0.001
Peak cTnI(mg/l)	43.20 ± 5.97	0.0 ± 0.00	< 0.001
LDH (mg/l)	1307.45 ± 1575.73	291.83 ± 64.84	< 0.001
CPK (mg/l)	1593.81 ± 2093.46	44.37 ± 32.37	< 0.001
CRP (mg/l)	7.38 ± 5.1	3.32 ± 1.29	< 0.001
CD (µmol of hydroperoxyde/mg of protein)	213.34 ± 86.5	88.05 ± 30.44	< 0.001
MDA (µM)	0.52 ± 0.23	0.33 ± 0.22	< 0.001
GPx(U/mg of protein)	24.55 ± 9.56	51.08 ± 11.08	< 0.001
Current Medications			
Statins, n (%)	216 (70.6)	0(0)	
Anti-aggregant, n (%)	271(88.6)	0(0)	
ACE-I, n (%)	269(87.9)	0(0)	

	NNSTEMI Patients (n = 306)	Healthy Controls (n = 410)	P
BETA-Blocker, n (%)	256(83.7)	0(0)	
Hypoglycemic drug, n (%)	248(81.1)	0(0)	
Fibrate, n (%)	198(64.7)	0(0)	

BMI: Body Mass Index; HR: Heart Rate; RPP: Rate pressure product; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; Creatine phosphokinase: CPK; Reactive protein C: CRP; Lactate dehydrogenase: LDH; cTnI: cardiac troponin T; MDA : Malondialdehyde; CD: Conjugated Diene; GPx: Glutathione Peroxidase .

The level of creatine phosphokinase (CPK), reactive protein C (CRP), and lactate dehydrogenase (LDH) were significantly higher in NSTEMI patients than in healthy controls (Table 1).

The serum ACE activity and the peak cTnI was significantly increased in NSTEMI patients ($p < 0.001$) (Fig. 1). We observed a statistically significant increase in malondialdehyde (MDA) and conjugated dienes (DC) in plasma in NSTEMI patients than in healthy controls ($p < 0.001$). The activity of glutathione peroxidase (GPx) in plasma was significantly lower in the plasma of patients than in healthy controls ($p < 0.001$) (Fig. 2).

The NSTEMI patients received anti-aggregant medication (88.6%), angiotensin-converting

enzyme inhibitor (ACE-I) (87.9%), beta-Blockers (83.7%), statins (70.6%) and fibrates medication (64.7%).

Pearson's correlation rank was then used to evaluate the correlations between diastolic BP, systolic BP, lipid profile, cardiac biomarkers, and other parameters in NSTEMI patients (as defined in Table 1).

In addition, a positive correlation was found between serum ACE activity and, total-cholesterol ($r = 0.129$; $p = 0.024$), cTnI ($r = 0.903$; $p = 0.001$), DC ($r = 0.940$; $p = 0.001$), MDA ($r = 0.488$; $p = 0.001$) and BMI ($r = 0.168$; $p = 0.003$) in NSTEMI patients. Serum ACE activity was negatively correlated to GPx ($r= -0.926$; $p = 0.001$) (Fig. 3).

The diastolic BP was correlated negatively with diabetes duration ($r= -0.128$; $p = 0.026$) and GPx activity ($r= -0.199$; $p = 0.001$), and positively with LDH ($r = 0,114$; $p = 0.047$), CPK ($r = 0,120$; $p = 0.036$), serum ACE activity ($r = 0,284$; $p = 0.001$), DC level ($r = 0.286$; $p = 0.001$), peak cTnI ($r = 0.181$; $p = 0.001$) and BMI ($r = 0.160$; $p = 0.005$) in NSTEMI patients.

The systolic BP was correlated positively to, smoking ($r = 0,155$; $p = 0.007$), LDL-cholesterol ($r = 0,124$; $p = 0.030$), serum ACE activity ($r = 0,114$; $p = 0.046$) and negatively with diabetes duration ($r= -0,125$; $p = 0.029$) in NSTEMI patients.

The rate pressure product (RPP) was correlated negatively with Fasting glucose (r= -0.144; p = 0.012), HbA1c (r= -0.117; p = 0.041) and GPx activity (r= -0.148; p = 0.009), and positively with smoking (r = 0,197; p = 0.001), BMI (r = 0,219; p = 0.001), peak cTnI (r = 0.131; p = 0.022), serum ACE activity (r = 0,190; p = 0.001) and DC level (r = 0.189; p = 0.001) in patients.

Regarding healthy controls, no correlation was found between the diastolic or systolic BP with serum ACE activity, peak cTnI, MDA, DC level, GPx activity, and lipid parameters.

Discussion

Control of blood pressure, lipid, and blood glucose levels are proven strategies in reducing the risk of cardiovascular complications [18]. All NSTEMI patients are hypertensive and diabetic. The fasting glucose, HbA1c, diastolic BP, and systolic BP are significantly higher in NSTEMI patients compared to controls. On other hand, lipid metabolism plays an important role in myocardial necrosis produced by ischemia[19]. we found that BMI, triglycerides, total cholesterol, LDL, and HDL cholesterol were significantly higher in NSTEMI patients than healthy controls. Changes in membrane cholesterol content affect its fluidity, permeability to ions, activities of membrane-bound enzymes, and increased degradation of phospholipids [20]. Smoking is identified as an independent risk factor in our study. In smokers patients, the risk of AMI is doubled and the benefits of changing other risk factors are significantly reduced [21]. Elevated Heart rate (HR) is frequently associated with high blood pressure and metabolic disorders and increases the risk of developing hypertension and diabetes [22]. Increased HR was found in NSTEMI patients. The HR product is a measure of the stress put on the cardiac muscle. A high HR is a risk factor for acute myocardial infarction in healthy people as well as in patients with heart disease [23].

The higher level of plasma troponin (cTn) found provides information about the severity of myocardial ischemia that caused cellular troponin degradation and release of troponin degradation products in the circulation. cTnI is expressed only in cardiac muscle, which allows these biomarkers to achieve extremely high specificity or myocardial damage[24]. Confirming our present results, we previously showed in a Tunisian population that higher serum ACE activity and elevated peak-cTnI levels might be clinically useful as markers to assess risk for myocardial infarction [3, 14]. Furthermore, we found that the glutathione peroxidase (GPx) was higher in healthy controls than NSTEMI patients. This result is in agreement with some studies which reported significantly decreased GPX activity[25–27]. Also, Serum ACE activity was negatively correlated to GPx.

In the same way, we found that the diastolic BP was correlated negatively to GPx activity, diabetes duration, and positively to serum ACE activity, DC level, peak cTnI, and BMI. The systolic BP was positively correlated to smoking, serum ACE activity, and cholesterol total and negatively to diabetes duration. So, a strong correlation of the diastolic or systolic BP and, serum ACE activity, troponin, peroxy, and oxy and lipid was found. This association is specific for NSTEMI patients since no correlation was found between the diastolic or systolic BP and all parameters in healthy controls.

The high rate pressure product (RPP) is an important indicator of increased oxygen demand. Moreover, we found that the rate pressure product (RPP) a significantly higher in NSTEMI patients compared to healthy controls, correlated negatively to GPx activity and positively to smoking, peak cTnI, serum ACE activity, and DC level. This suggests the existence of elevated damage to the lipid component of the cell-mediated by free radicals which suggest their involvement in the pathogenesis of NSTEMI.

HR is related to the extent of atherosclerosis [28]. Then, higher HR, RPP, the diastolic and systolic BP values indicate increased use of myocardial oxygen and increase the NSTEMI risk. Systolic BP is known to increase the oxygen demand of the myocardium [29]. HR represents the interaction of diastolic, systolic BP, pulse wave reflection, reduced systolic vascular reservoir, and ejection volume [30].

Tissue changes that occur in the myocardium are related to the extent to which the cells have been deprived of oxygen. When myocardial cells are damaged or destroyed due to deficient oxygen supply or glucose, the cell membrane becomes permeable or may rupture, which results in the leakage of enzymes. The association between circulating lipids and oxidative damage markers in the blood is mostly on health consequences and particularly on vascular diseases[31]. Oxidation of fatty acids leads to the generation of CD, which reflects plasma lipids peroxidation. MDA, a final product of lipid peroxidation, is the most commonly measured biomarker of oxidative stress [32]. The increase in ACE activity could lead to increased activity of nicotinamide adenine dinucleotide phosphate oxidase [33, 34] which could, in turn, increase the release of ROS [35–37] such as superoxide radical (O_2-) and H_2O_2, which are involved in diverse signaling functions that may impair ventricular microvascular blood flow causing myocardial ischemia, cTnI-release, and ventricular dysfunction. [38, 39] ROS can rapidly react with NO, leading to peroxynitrite formation, reduced NO bioavailability increasing vascular reactivity [40]. NO prevents platelet aggregation and activation of several cells (particularly monocytes, which are transformed into macrophages containing lipids) and inhibits proliferation of smooth muscle cells, which are integral components of atherosclerotic vascular lesions and stimulants of ROS and oxidative stress. Although the effect of Ang II on ROS production is becoming clearer, there is still a paucity of knowledge of its mechanism and how these redox-sensitive processes lead to vascular inflammation and fibrosis, and what factors act as damaging stress signals to induce vascular injury. Despite the number of patients is small in this study, further studies are necessary to confirm our results.

Conclusion

Our results suggest the existence of a strong correlation between the rate pressure product, diastolic and systolic BP and, lipid profile, cardiac biomarkers, and serum angiotensin-converting enzyme activity, oxidative stress (MDA, DC) and antioxidant status (GPx) increases the NSTEMI risk on patients.

Declarations

Funding

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Author contributions

All authors read and approved the fnal manuscript. Sounira Mehri: written manuscript; Sonia Hammami: contributed to the study conception and design. Raja chaaba and wided khamlaoui: sample collection, data collection and statistical analysis. Mohammed Hhammami: revision of the manuscript.

Compliance with ethical standards

Conflict of interest

No potential conflict of interest was reported by the authors.

Ethical approval

Not applicable

Consent to participate

Not applicable

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Figures

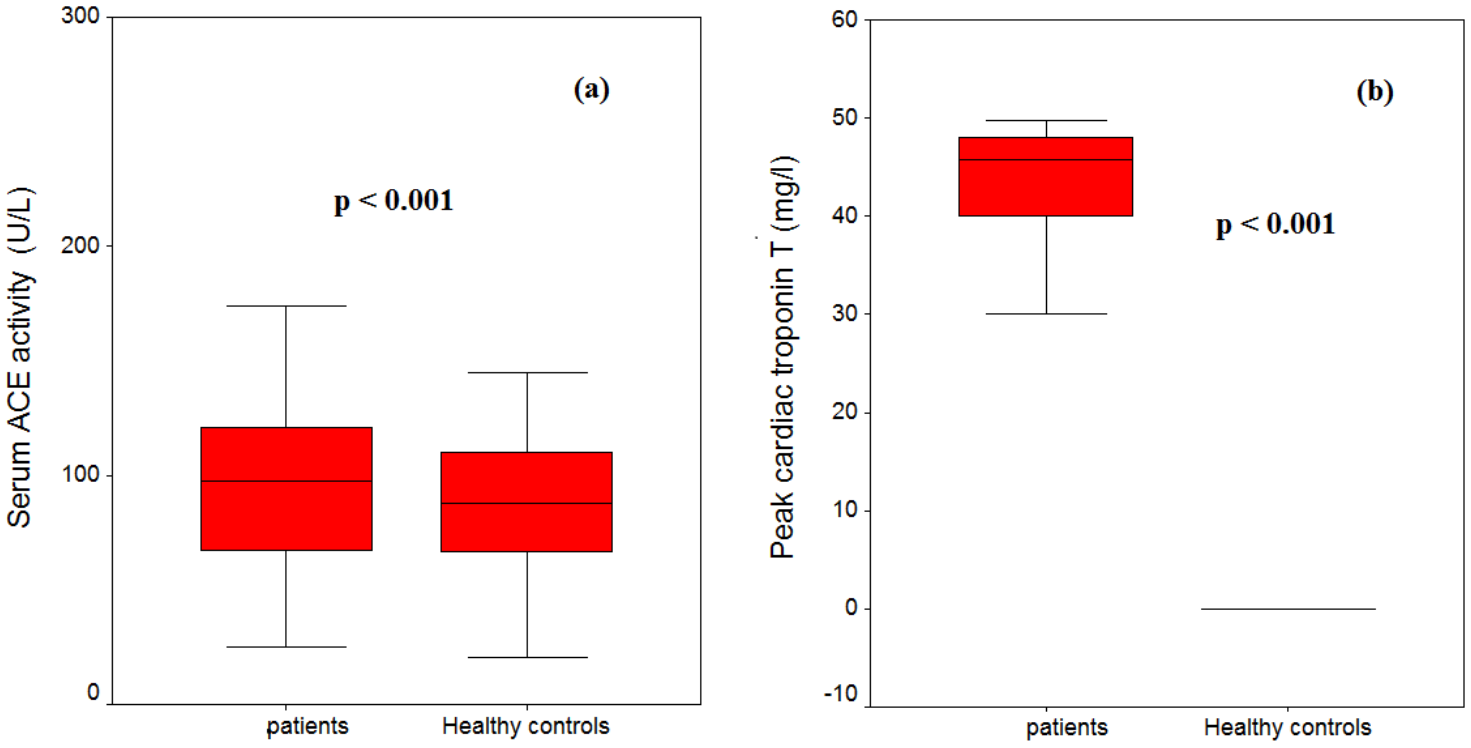

Figure 1

Box plot displaying the distribution of the (a) serum ACE activity and (b) cardiac troponin T (cTnI) in patients compared to healthy controls.

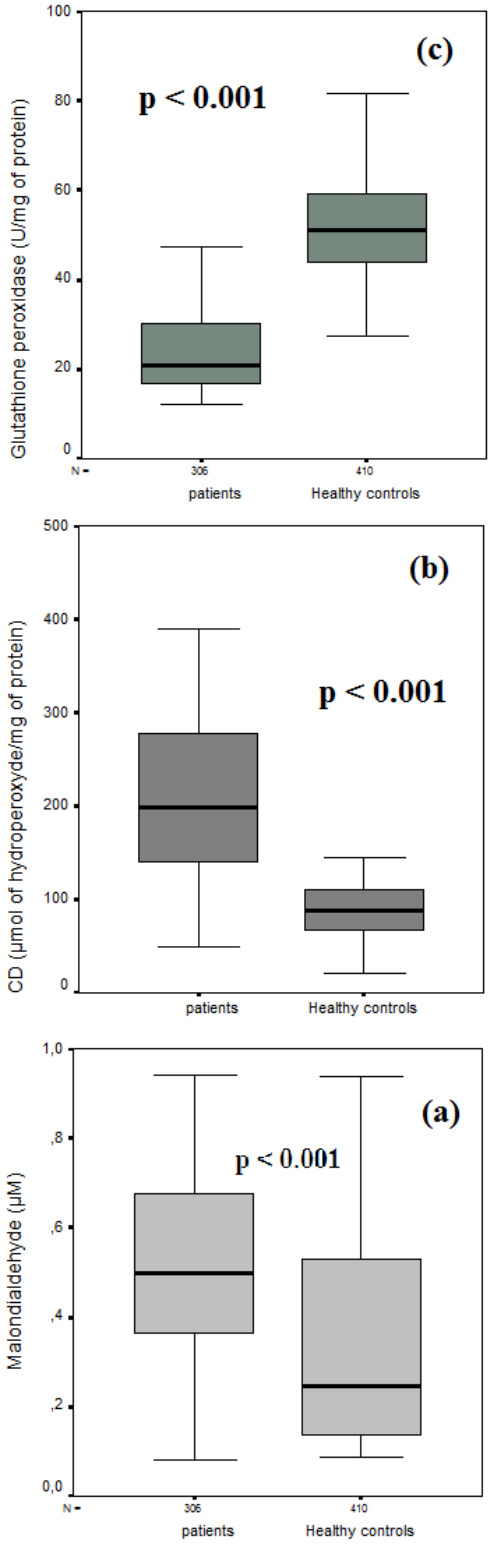

Figure 2

Box plot displaying the distribution of lipid peroxidation markers (a) malondialdehyde (MDA), (b) conjugated dienes (DC), and the antioxidant enzyme glutathione peroxidase (GPx) in patients and healthy controls.

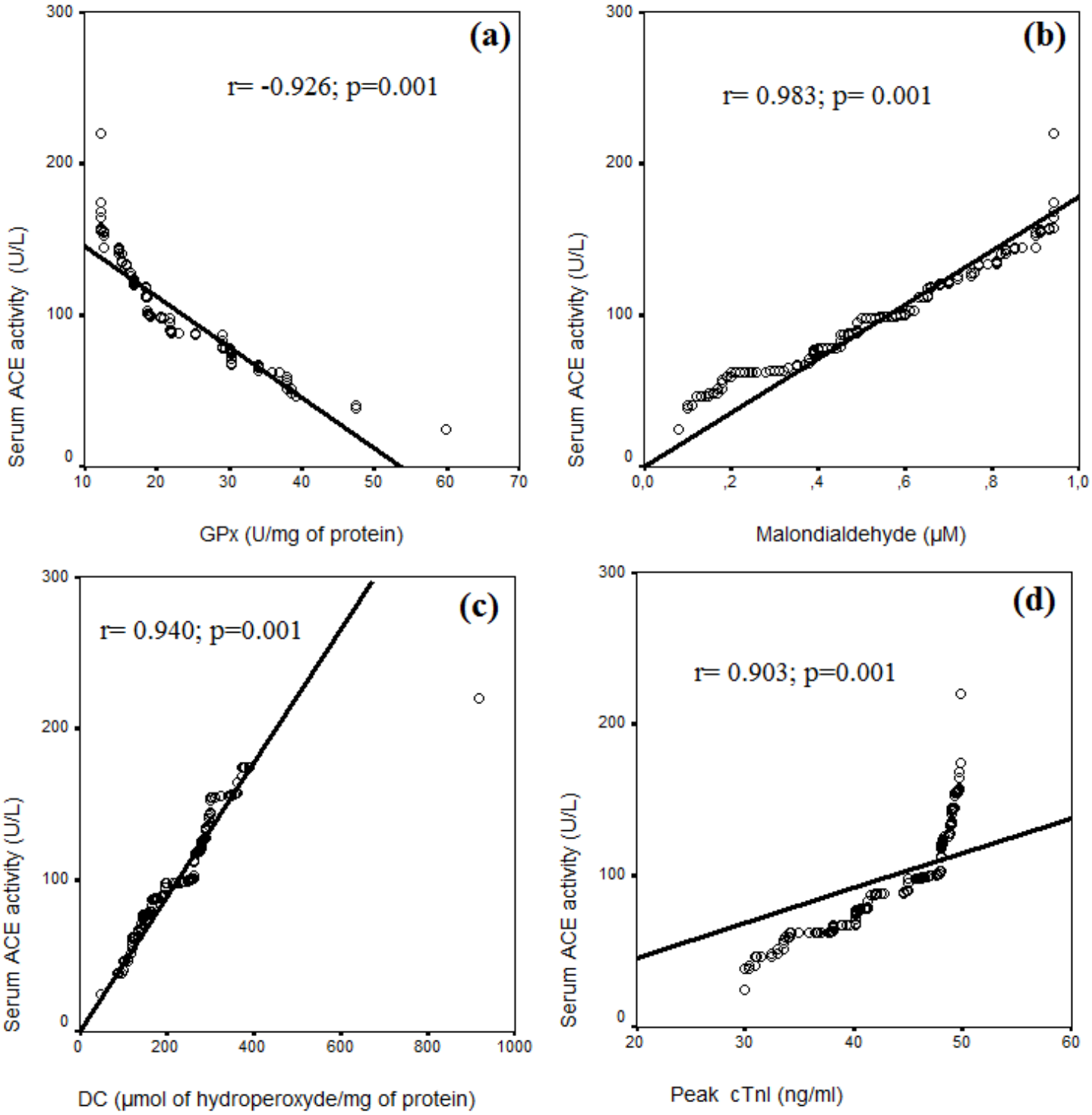

Figure 3

Scatterplot illustrating the correlation between Serum ACE activity and (a) GPx (r= -0.926; p=0.001); (b) MDA (r= 0.983; p=0.001); (c) DC (r= 0.940; p= 0.001); (d) cTnI (r= 0.903; p=0.001) in NSTEMI patients.