OXIDIZED LOW DENSITY LIPOPROTEIN AND HIGH SENSITIVE C-REACTIVE PROTEIN IN NON-DIABETIC, PRE-DIABETIC AND DIABETIC PATIENTS IN THE ACUTE PHASE OF THE FIRST MYOCARDIAL INFARCTION TREATED BY PRIMARY PERCUTANEOUS CORONARY INTERVENTION

OKSIDOVANI LIPOPROTEIN NISKE GUSTINE I VISOKOSENZITIVNI C-REAKTIVNI PROTEIN KOD NEDIJABETIČARA, PREDIJABETIČARA I DIJABETIČARA U AKUTNOJ FAZI PRVOG INFARKTA MIOKARDA LEČENOG PRIMARNOM PERKUTANOM KORONARNOM INTERVENCIJOM

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Summary

Background: Oxidized low density lipoprotein (ox-LDL) and high-sensitive C-reactive protein (hs-CRP) are elevated in diabetes mellitus (DM) and associated with accelerated atherosclerosis. Little is known about their dynamics in the acute phase of ST segment elevation myocardial infarction (STEMI), especially in relation to the presence of DM and pre-diabetes (pre-DM). This study aimed to analyze time-dependent changes in ox-LDL and hs-CRP regarding the presence of pre-DM and DM in STEMI patients treated by primary percutaneous coronary intervention (pPCI).

Methods: In 103 consecutive patients with the first anterior STEMI ox-LDL and hs-CRP were measured before pPCI, on day 2 and day 7 after pPCI.

Results: Patients were classified into: non-diabetics, pre-diabetics and diabetics. In each group the maximal ox-LDL concentration was found on admission, decreased on day 2 and

Kratak sadržaj

Uvod: Oksidovani lipoprotein niske gustine (ox-LDL) i visokosenzitivni C-reaktivni protein (hs-CRP) povišeni su u dijabetes melitusu (DM) i povezani sa ubrzanom aterosklerozom. Malo je poznata njihova dinamika u akutnoj fazi infarkta miokarda sa elevacijom ST segmenta (STEMI), naročito u zavisnosti od prisustva DM ili predijabetesa (pre-DM). Ova studija je analizirala promenu koncentracija ox-LDL i hs-CRP u akutnoj fazi STEMI u odnosu na prisustvo pre-DM i DM kod bolesnika lečenih primarnom perkutanom koronarnom intervencijom (pPKI).

Metode: Kod 103 konsekutivna bolesnika sa prvim prednjim STEMI, hs-CRP i ox-LDL mereni su pre pPCI, drugog i sedmog dana nakon pPKI.

Rezultati: Bolesnici su podeljeni u tri grupe: nedijabetičari, predijabetičari i dijabetičari. U svakoj grupi maksimalna koncentracija ox-LDL bila je na prijemu, smanjivala se dru-

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reached the lowest values on day 7 (p<0.001). Diabetics had the highest ox-LDL concentrations compared to pre-diabetics and non-diabetics (on admission: p=0.028, on day 2: p=0.056, on day 7: p=0.004). hs-CRP concentration rose from admission, reached its peak on day 2 and decreased on day 7, in each group (p<0.001). Significant differences in hs-CRP concentrations were found between non-diabetics and pre-diabetics on admission (p=0.018) and day 2 (p=0.026). In a multivariate analysis DM was an independent determinant of high ox-LDL concentrations. Both ox-LDL and hs-CRP significantly correlated with Killip class, left ventricular ejection fraction, NT-proBNP and peak troponin I.

Conclusions: In patients with the first STEMI treated by pPCI there were significant differences in ox-LDL and hs-CRP concentrations between non-diabetics, pre-diabetics and diabetics. Ox-LDL and hs-CRP concentrations were related to heart failure parameters.

Keywords: oxidized LDL, high-sensitive C-reactive protein, acute myocardial infarction, diabetes mellitus

gog dana i postizala najniže vrednosti sedmog dana (p<0,001). Dijabetičari su uvek imali najviše vrednosti ox-LDL u poređenju sa predijabetičarima i nedijabetičarima (na prijemu: p=0,028, drugog dana: p=0,056 i sedmog dana: p=0,004). Koncentracija hs-CRP je u svakoj grupi rasla od prijema, postizala maksimalne vrednosti drugog dana i smanjivala se sedmog dana (p<0,001). Značajna razlika u koncentraciji hs-CRP između nedijabetičara i predijabetičara registrovana je na prijemu (p=0,018) i drugog dana (p=0,026). U multivarijantnoj analizi DM je bio nezavisan prediktor visokih koncentracija ox-LDL. I ox-LDL i hs-CRP su značajno korelisali sa Killip klasom, ejekcionom frakcijom leve komore, koncentracijom NT-proBNP i maksimalnom vrednošću troponina I.

Zaključak: Kod bolesnika sa prvim STEMI lečenim pPKI postojale su značajne razlike u koncentraciji ox-LDL i hs-CRP između nedijabetičara, predijabetičara i dijabetičara. Koncentracije ox-LDL i hs-CRP značajno su korelisale sa parametrima srčane insuficijencije.

Ključne reči: oksidovani LDL, visokosenzitivni C-reaktivni protein, akutni infarkt miokarda, dijabetes melitus

Introduction

Inflammation and oxidative stress within the vascular wall represent key processes in the continuum of coronary atherosclerosis: from plaque formation, to plaque instability and rupture inducing acute myocardial infarction, reperfusion injury after treatment and reparation and tissue healing (1).

C-reactive protein is an acute phase protein produced in the liver that appears in the circulation in response to inflammatory cytokines. High-sensitive C-reactive protein (hs-CRP) is one of the most studied biochemical markers of atherosclerosis and a sensitive marker of increased inflammatory activity within the arterial wall (1, 2). It is elevated in patients with diabetes mellitus (DM), proportionally to the insulin resistance and/or beta cells dysfunction (3), and can be used for cardiovascular risk assessment (4). In patients with the acute ST segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (pPCI) hs-CRP predicts long term mortality, re-infarction and adverse events (5).

The oxidatively modified form of low density lipoprotein (ox-LDL) is a proinflammatory and pro-atherogenic particle containing free radicals that plays a critical role in atherosclerosis (6). Ox-LDL causes injury to endothelial cells via several complex mechanisms (7–13), acts as a monocyte chemoattractant, impairs the motility of tissue macrophages and induces platelet adhesion (7). Furthermore, ox-LDL in the experimental studies had a devastating effect on myocardial cells, inducing damage and irregular electrical activity similar to other oxidative stress-generating systems (14). Ox-LDL is increased in DM contributing to accelerated atherosclerosis (15). A high level of circulating ox-LDL is an inde-

pendent and significant predictor of future cardiac events in type 2 diabetic patients with chronic coronary artery disease (16). In patients with acute coronary syndrome ox-LDL concentration correlates well with the severity of acute coronary syndrome (17), with the level of hs-CRP (18) and predicts late stent restenosis after pPCI (19).

However, plasma kinetics of ox-LDL in the acute phase of STEMI after mechanical reperfusion and its relation to the level of inflammation is unclear regarding the presence of DM and pre-diabetes (pre-DM). The aim of this study was to evaluate time-dependent changes in ox-LDL and hs-CRP concentrations in STEMI patients treated by pPCI in relation to the presence of DM and pre-DM. We also evaluated relationships between ox-LDL and hs-CRP and left ventricular contractility and heart failure.

Materials and Methods

Patient population

A total of 103 consecutive patients with the first anterior STEMI treated by pPCI were enrolled in the study from the end of November 2009 to the end of December 2010. The inclusion criteria for this prospective, single center, observational study included recanalization of the left anterior descending artery (LAD) with visually assessed residual stenosis <30%. The STEMI was defined and treated according to ESC guidelines (20). The exclusion criteria were: (1) inability or refusal to provide written informed consent; (2) acute or chronic inflammation or infection (3), a history of autoimmune, malignant disease, liver, kidney or thyroid diseases. The Ethical Committee of our hospital approved the study protocol. Anthropometric parameters including weight and height

were measured for all patients, and their body mass index was calculated as the ratio of weight to height squared. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive treatment. DM and pre-DM were defined according to the American Diabetes Association (ADA) 2014 guidelines (21). Patients were considered smokers if they smoked ≥1 cigarette/day at the time of admission or in the preceding 12 months. Clinical manifestation of the heart failure on admission was assessed by Killip class (Killip 1, no heart failure; Killip 2, S3 and/or basal lung crepitations; Killip 3, acute pulmonary edema; Killip 4, cardiac shock).

Blood sampling and biochemical analysis

When a diagnosis of STEMI was established and a decision to perform pPCI was made, blood samples were obtained from peripheral vein before starting intervention, and 4 h, 8 h, 12 h, 18 h, 24 h, 48 h (2nd day) and 168 h (7th day) after intervention. Blood samples for troponin I (TnI), MB fraction of creatine kinase (CK-MB), N-terminal pro-brain natriuretic peptide (NT-proBNP), and high-sensitive C-reactive protein (hs-CRP) determination were allowed to coagulate at room temperature for 30 min, and then centrifuged at 4000 rpm for 10 min to obtain serum samples. Serum TnI and CK-MB were measured by chemiluminescent microparticle immunoassay (CMIA) on the Architect i2000 System. The serum levels of NT-proBNP were measured by a Roche Cobas 6000 automated analyzer (Roche Diagnostics, Mannheim, Germany). The serum hs-CRP concentrations were measured in blood samples on admission, on the 2nd and 7th day by means of the immuno-turbidimetric test (Olympus Life and Material Science Europe GmbH, Ireland) on an Olympus AU 400 analyzer. The lowest detectable level was 0.02 mg/L. Ox-LDL measurement in EDTA plasma from blood samples on admission, on the 2nd and 7th day was performed using a Mercodia ELISA assay (Mercodia AB, Uppsala, Sweden). In this solid-phase two-site enzyme immunoassay two monoclonal antibodies are directed against separate antigenic determinants on the oxidized apolipoprotein B molecule. The detection limit is <1 mU/L. The intrassay and interassay coefficients of variation were 6.3% and 8%, respectively. Other biochemical and hematologic measurements involved the use of standard assays. The estimated glomerular filtration rate (eGFR) was calculated using an abbreviated Modification of Diet in Renal Disease study formula (22).

Primary PCI

PCI was performed within 12 h from the onset of chest pain by experienced interventionists. In all patients, stent was successfully implanted in LAD.

Angiographic Thrombolysis In Myocardial Infarction (TIMI) flow grade was evaluated as described previously (23). Slow/no-reflow was defined as TIMI ≤2 after PCI. All patients and their angiograms were graded according to the number of diseased coronary arteries. A coronary artery was considered diseased if there was any obstructive lesion ≥70% in diameter in that artery or one of its major branches (diameter ≥2.5 mm). Medication used in the acute phase included loading a 600 mg dose of clopidogrel and 300 mg of aspirin and an intravenous bolus of heparin before pPCI, followed by dual antiplatelet therapy (clopidogrel or ticlopidine and aspirin) and statins in all patients. Glycoprotein IIb/IIIa inhibitor, thrombectomy and intracoronary vasodilatators were administered at the discretion of the interventional cardiologist.

Statistical analysis

Normality distribution of the analyzed continuous variables was assessed with the Kolmogorov–Smirnov test. Normally distributed continuous variables are expressed with mean ± SD, and continuous variables that did not show normal distribution are expressed as the median value and interquartile range (25th, 75th percentile). Categorical data are shown as frequencies and percentages. Related-samples Friedman's two ways ANOVA by ranks was used to test time-dependent changes in hs-CRP and ox-LDL concentrations. Spearman's rank correlation coefficients were used to assess the relationships between hs-CRP and ox-LDL concentrations and others variables. Binary logistic regression analysis was used to assess determinants of ox-LDL concentrations and hs-CRP concentrations higher than the 75th percentile on admission, on the 2nd and 7th day. All variables with p less than 0.05 from univariate analysis entered multivariate analysis (Wald method). Results are expressed as the odds ratios (OR) and their 95% confidence intervals (CI) per one standard deviation increment of each measure. The statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 20.0 (SPSS, Inc., Chicago). Statistical significance was defined as $p < 0.05$.

Results

Risk factors, clinical characteristics and baseline biochemical variables are presented in *Table I*. The mean age of patients was 60 years and 73% were male. They were predominately nonsmokers (65%) and hypertensive (65.7%). Twenty-five percent of patients had DM, 35% had pre-DM and 40% did not have DM or pre-DM. Among the patients, 42.7% had hypercholesterolemia and 63% had a BMI>25 kg/m². The median time from symptom onset to balloon (pPCI intervention) was 4.1 h. On admission, 67% of the patients were in Killip class one, 28% in class two

Table I Baseline characteristics.

N	103
Risk factors	
Age (years)	59.01±11.90
Male (%)	73
Body Mass Index (kg/m^2)	26.51±3.28
Waist circumference (cm)	96.10±11.34
Hypertension (%)	65.7
Diabetes (%)	25.0
Pre-diabetes (%)	35.0
Without diabetes or pre-diabetes (%)	40.0
Hypercholesterolemia (%)	44.6
Smokers (%)	35.1
Laboratory findings	
Hemoglobin (g/L)	146.10±14.21
WBC count (×10^9/L)	12.39±3.66
Neutrophil count (×10^9/L)	8.06±4.86
Erythrocytes (×10^{12}/L)	4.48±0.46
Platelets (×10^9/L)	232±61
Fibrinogen (g/L)	4.01±1.07
Albumin (g/L)	43.26±5.14
Ferritin (μg/L)	163.91±110.47
Glucose (mmol/L)	9.09±3.40
HbA1c (%)	6.14±1.26
Uric acid (μmol/L)	292.62±73.27
eGFR (mL/min)	96.59±32.87
TnI (μg/L)	0.56 (0.09–5.23)
CK-MB (μg/L)	8.2 (3.1–35.8)
NT-proBNP (pg/mL) (ng/L)	279.4 (126.00–1011.00)
Total cholesterol (mmol/L)	6.19±1.30
HDL cholesterol (mmol/L)	1.20±0.38
LDL cholesterol (mmol/L)	4.10±1.16
Triglycerides (mmol/L)	1.49 (1.12–1.30)
Apo AI (g/L)	1.43±0.27
Apo B (g/L)	1.13±0.29
Clinical features	
Time from chest pain onset to balloon (min)	248 (161–330)
Killip class 1/2/3/4 on admission (%)	67/28/5/0
Left ventricular ejection fraction – EF (%)	48.1±10.0
1/2/3 vessel disease (%)	63/15/22
Number of implanted stents	1 (1.3)
Bare metal stent (%)	75
Slow flow / no reflow (i.e. TIMI flow grade ≤2) after pPCI (%)	13
In-hospital mortality (%)	5.8

Table II Time-dependent changes in ox-LDL and hs-CRP concentrations.

	All patients (n=103)	No-DM (n=41)	Pre-DM (n=36)	DM (n=26)	p
ox-LDL (U/L)					
Admission	102.00 (84.48–118.32)	65.94* (53.25-86.46)	49.00* (38.17–63.50)	113.11 (96.00–167.00)	0.028
2nd day	65.94 (53.25–86.46)	62.00* (51.30–79.40)	44.31* (36.18–51.00)	44.31* (36.18–51.00)	0.056
7th day	49.00 (38.17–63.50)	44.31* (36.18–51.00)	52.49* (38.05–61.00)	58.00 (48.00–88.57)	0.004
hs-CRP (mg/L)					
Admission	3.46 (1.40–9.95)	2.20 (1.15–4.0)	4.80† (2.03–10.70)	7.35 † (3.13–32.70)	0.001
2nd day	49.30 (23.70–116.00)	32.40 (17.63–93.78)	58.3† (34.2–158.00)	52.60† (26.60–123.74)	0.059
7th day	18.21 (7.90–52.78)	11.80 (6.90–33.90)	20.60 (9.80–70.18)	24.10† (6.9–67.54)	0.258

* p<0.05 compared to DM   † p<0.05 compared to no-DM

Table III Time-dependent changes in plasma lipid and lipoprotein concentrations.

	All patients (n=103)	No-DM (n=41)	Pre-DM (n=36)	DM (n=26)	p
Total cholesterol (mmol/L)					
Admission	6.19±1.30	6.08±1.21	6.03±1.00	6.32±1.41	0.632
2nd day	5.10±1.07	5.15±1.14	4.88±0.74	5.33±1.27	0.288
7th day	4.31±0.95	4.27±0.88	4.19±0.70	4.49±1.11	0.448
HDL cholesterol (mmol/L)					
Admission	1.20±0.38	1.25±0.42	1.21±0.29	1.08±0.43	0.234
2nd day	1.09±0.25	1.11±0.29	1.12±0.23	1.00±0.21	0.161
7th day	0.90±0.21	0.87±0.21	0.93±0.26	0.88±0.18	0.412
LDL cholesterol (mmol/L)					
Admission	4.10±1.16	4.02±1.05	3.95±0.84	4.21±1.38	0.674
2nd day	3.23±0.91	3.23±1.01	3.07±0.61	3.39±0.98	0.398
7th day	2.72±0.90	2.77±0.79	2.56±0.69	2.77±0.92	0.543
TG (mmol/L)					
Admission	1.49 (1.12–1.30)	1.44 (1.09–2.32)	1.53 (1.19–1.95)	1.57 (1.11–2.29)	0.946
2nd day	1.60 (1.27–2.00)	1.61* (1.37–1.97)	1.42* (1.17–1.76)	1.81 (1.44–2.78)	0.013
7th day	1.39 (1.16–1.84)	1.34* (1.06–1.60)	1.38* (1.06–1.84)	1.58 (1.39–2.09)	0.022
Apo AI (mmol/L)					
Admission	1.43±0.27	1.45±0.31	1.42±0.25	1.42±0.22	0.878
2nd day	1.28±0.21	1.30±0.22	1.30±0.20	1.16±0.17	0.104
7th day	1.13±0.22	1.12±0.20	1.15±0.24	1.10±0.17	0.841
Apo B (mmol/L)					
Admission	1.13±0.29	1.12±30	1.05±0.21	1.20±0.28	0.137
2nd day	1.03±0.26	0.99±0.25*	1.10±0.21*	1.21±0.30	0.033
7th day	0.89±0.21	0.87±0.20*	0.85±0.16*	1.01±0.24	0.045

* p<0.05 compared to DM   † p<0.05 compared to no-DM

Table IV Correlations between ox-LDL and hs-CRP concentrations and clinical and biochemical parameters.

	ox-LDL on admission	ox-LDL 2nd day	ox-LDL 7th day	hs-CRP on admission	hs-CRP 2nd day	hs-CRP 7th day
Glucose on admission	0.158	0.194	0.269*	0.175	0.334**	0.158
HbA1c	0.311**	0.262*	0.365**	0.400**	0.279*	0.220*
WBC on admission	0.150	0.045	0.070	0.130	0.471**	0.373**
Neutrophils on admission	0.105	–0.019	0.042	0.124	0.399**	0.265**
NT-proBNP on admission	0.242*	0.252*	0.258*	0.417**	0.213*	0.280**
NT-pro BNP 2nd day	0.241	0.200	0.242	0.263*	0.533**	0.394**
NT-pro BNP 7th day	0.254	0.294*	0.211	0.427**	0.484**	0.549**
hs-CRP on admission	0.183	0.220*	0.256*	–	–	–
hs-CRP 2nd day	0.145	0.220*	0.259*	–	–	–
hs-CRP 7th day	0.073	0.169	0.184	–	–	–
HDL 7th day	–0.217*	–0.203*	–0.141	–0.142	–0.222*	–0.156
Apo AI 2nd day	–0.284*	–0.356*	–0.232	–0.239*	–0.140	–0.027
Apo AI 7th day	–0.388**	–0.458**	–0.372**	–0.317*	–0.395**	–0.355**
TnI peak	0.252*	0.101	–0.064	0.117	0.379**	0.462**
No-DM/pre-DM/DM	0.285**	0.267*	0.370**	0.378**	0.213*	0.143
Killip class	0.249*	0.242*	0.191*	0.290**	0.472**	0.304**
LVEF	-0.335**	–0.291*	–0.260*	–0.115	–0.380**	–0.229*

and 5% in class three. The peak concentration of TnI was 88.27 (29.48–167.91) µg/L. The concentrations of NT-proBNP (pg/mL) (ng/L) were as follows: on admission 290.05 (126.10–1039.50), on the 2nd day 3170 (1201–4990) and on the 7th day 1237.50 (489.63–2576.75).

Time-dependent changes in ox-LDL and hs-CRP in the whole study group and comparisons between patients with non-DM vs pre-DM vs DM are presented in *Table 2*. In the whole group and in each of the three subgroups changes in ox-LDL concentration were statistically significant and showed the same pattern: maximal on admission, decreased on the 2nd day and minimal on the 7th day (p<0.001, for each group). At each time point diabetics had the highest ox-LDL concentrations compared to no-DM and pre-DM groups (on admission: p=0.028, on day 2: p=0.056, on day 7: p=0.004), whereas differences between no-DM and pre-DM groups were insignificant.

Time-dependent changes in hs-CRP concentrations were also significant and showed the same pattern within each group: hs-CRP concentrations rose from admission, reached peak values on the 2nd day and decreased on the 7th day, but to levels above the start values (p<0.001) (*Table II*). Diabetics had all hs-CRP concentrations statistically significantly higher compared to non-diabetics. The differences between non-diabetics and pre-diabetics were significant on admission (p=0.010) and on the 2nd day (p=0.026), whereas differences between pre-diabetics and diabetics were not significant (*Table II*).

Time-dependent changes in plasma lipid and lipoprotein concentrations with comparisons between non-diabetics, pre-diabetics and diabetics are presented in *Table III*.

Correlations between ox-LDL and hs-CRP concentrations and the biochemical and clinical parameters are presented in *Table IV*. Ox-LDL concentrations did not correlate with LDL levels. In the multivariate logistic regression analysis, independent determinants for ox-LDL concentration higher than the 75th percentile on admission were diabetes mellitus (OR 8.013, 95% CI 1.735–36.999, p=0.008) and peak TnI (OR 4.004, 95% CI 1.566–10.241, p=0.004), on the 2nd day diabetes mellitus (OR 10.741, 95% CI

2.394–48.191, p=0.002) and peak TnI (OR 2.333, 95% CI 1.063–5.123, p=0.035), and on the 7th day diabetes mellitus (OR 12.006, 95% CI 1.575–91.503, p=0.016) and Killip class (OR 12.006, 95% CI 1.120–33.840, p=0.037). In the multivariate logistic regression analysis independent predictors of hs-CRP concentration higher than the 75th percentile on admission were NT-proBNP concentration on admission (OR 3.312, 95% CI 1.462–9.990, p=0.006), on the 2nd day Killip class (OR 18.446, 95% CI 3.057–111.321, p=0.001), glucose on admission (OR 1.535, 95% 1.024–2.332, p=0.038), WBC count on admission (OR 2.798, 95% CI 1.060–7.383, p=0.038) and 2nd day NT-proBNP concentration (OR 4.914, 95% CI 1.714–14.090, p=0.003), and NT-proBNP concentration on the 7th day (OR 15.712, 95% CI 2.647–93.285, p=0.002). DM and pre-DM were significant predictors of hs-CRP concentrations in univariate, but not in multivariate analyses.

Discussion

To the best of our knowledge, the present study is the first to analyze the dynamics of ox-LDL and hs-CRP plasma concentrations regarding the presence of DM, pre-DM and no diabetes in the acute phase of the first myocardial infarction treated by primary percutaneous coronary intervention. It has allowed us to make several inferences. First, time-dependent changes in the ox-LDL concentration are similar regardless of the presence of DM or pre-DM, with the highest values on admission and a gradual fall towards the 7th day. However, patients with diabetes had significantly higher levels of ox-LDL before and after pPCI compared to pre-diabetics and non-diabetics. Second, the independent determinants of plasma ox-LDL concentrations in the acute STEMI phase were DM, peak TnI and Killip class. Third, the dynamics of hs-CRP concentration during the acute STEMI phase is uniform apart from the presence of DM or pre-DM, with the lowest values on admission and peak on the 2nd day after pPCI. Nevertheless, not only diabetics but also pre-diabetics had significantly higher hs-CRP concentrations compared to non-diabetics. Fourth, both ox-LDL and hs-CRP levels were significantly associated with the heart failure parameters, including Killip class, left ventricular ejection fraction and NT-proBNP.

Previous studies evaluating the association between plasma ox-LDL concentration and acute coronary syndrome revealed higher levels of ox-LDL in more severe clinical forms of acute coronary syndrome (24–26). Data regarding the plasma kinetics of ox-LDL in patients with acute myocardial infarction treated by prim PCI are scarce and results strongly depend on the methodology used for the ox-LDL assay. In the prospective study by Tsmikas et al. (27) minimal ox-LDL measured by the antibody E06

(OxLDL-E06), determining the content of oxidized phospholipids per apolipoprotein B-100, increased at hospital discharge and at 30 days in patients with myocardial infarction and decreased towards the baseline over the next 7 months. Also, a rapid transient increment in ox-LDL concentration immediately after pPCI was reported following elective percutaneous coronary intervention in patients with stable angina pectoris (28). We, as others (19, 29), found the maximal values of ox-LDL before pPCI and then a gradual decrement on the 2nd and further on the 7th day. This pattern of plasma kinetics is in accordance with the concept that plaque rupture is followed by release of ox-LDL particles from the vascular wall or oxidized phospholipids that bind to circulating LDL and cause an increment in plasma ox-LDL. In previous studies (28), release of ox-LDL resulted in immune complex formation with ultimate clearance of these particles that could explain the decrement of ox-LDL concentration in the days following pPCI found in the current study.

The main finding of our study is that diabetics in the acute STEMI phase before and during the first week after pPCI have higher plasma ox-LDL concentrations compared to pre-diabetics and non-diabetics. Several studies have shown increased oxidative stress in diabetes with increased values of ox-LDL compared to non-diabetics (15, 30), but to the best of our knowledge, this is the first study confirming that diabetics have increased ox-LDL in the acute STEMI phase compared to both non-diabetics and pre-diabetics. In chronic states, serum levels of ox-LDL were found to be significantly increased in patients with impaired glucose tolerance (pre-diabetes) compared to individuals with normal glucose tolerance (31). In the current study, in the acute phase of STEMI, we could not find a significant difference in serum ox-LDL concentrations between non-diabetics and pre-diabetics.

Previous studies have identified body mass index (30), percent of visceral fat (30), and duration of diabetes (15) as important determinants of the ox-LDL concentration. In our study, plasma ox-LDL concentrations in STEMI patients did not correlate with BMI, or with waist circumferences, suggesting that in the acute STEMI these parameters might not be crucial for the level of oxidative modification of LDL. Whereas glucose concentration on admission was not a determinant of the ox-LDL plasma concentration, presence of DM and quality of glucose metabolic control in the past several months, i.e. HbA1c were. Furthermore, DM was the only investigated parameter that was a significant and independent predictor of high ox-LDL concentrations in the multivariate analysis, for all three time points. These data strongly suggest the importance of DM with regard to oxidative stress during the acute STEMI.

The relationships between ox-LDL and other plasma lipid fractions in chronic stable patients were previously investigated. In patients with impaired fasting glucose (IGF) (pre-diabetes) a strong correlation was detected between ox-LDL and LDL cholesterol and triglycerides indicating that LDL oxidation in IGF is preferentially associated with dyslipidemia (31). In older individuals determinants of ox-LDL in the multivariate analysis were LDL cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol (33). In the current study, in the acute STEMI phase ox-LDL did not correlate well with LDL concentration, but was significantly inversely related to HDL cholesterol and apolipoprotein AI (Apo AI) concentrations. HDL and ox-LDL are antagonists in atherothrombosis (34). Their mutual interactions in the acute phase of STEMI were not investigated. HDL-associated enzyme paraoxonase that inhibits the oxidation of LDL and PAF-acetyl hydrolase, which circulates in association with HDL and degrades bioactive oxidized phospholipids, could be potential parameters explaining the inverse relation between ox-LDL and HDL concentrations in our study group. Apo AI, a major protein component of HDL, promotes fat efflux, including cholesterol, from tissues to the liver for excretion. In our study, Apo AI concentration in STEMI patients significantly inversely correlated with ox-LDL and this relation has not been previously described.

It has been suggested that oxidative stress and chronic inflammation during atherosclerosis are mutually coupled processes (1). The results of our study – the positive correlation between ox-LDL and hs-CRP concentrations in acute STEMI patients – are in agreement with the recently published data (18). Data regarding the potential mechanisms connecting plasma ox-LDL and hs-CRP concentrations in the acute STEMI phase are scarce. In experimental models, C-reactive protein binds to oxidized LDL through recognition of a ligand phosphorylcholine of oxidized phospholipids (34), as part of the innate immune response to oxidized phospholipids within ox-LDL. C-reactive protein also promotes ox-LDL uptake in macrophages (35). In our study, correlations between hs-CRP and ox-LDL concentrations during the STEMI course showed that the level of inflammation and increment in serum hs-CRP concentration after pPCI are proportional to the plasma ox-LDL concentration before pPCI.

Previous studies evaluating the clinical relevance of circulating ox-LDL concentration in STEMI patients treated by pPCI predominately explored whether ox-LDL can predict stent restenosis during the follow-up (29). To the best of our knowledge, our study is the first connecting the level of plasma ox-LDL with acute heart failure. In our study, ox-LDL was associated with the Killip class on admission, NT-pro BNP and left ventricular ejection fraction. Furthermore, ox-LDL on admission was related to the traditional marker of infarct size, peak value of TnI, independently from other covariates. In previous studies, plasma ox-LDL

was reported to be related to the NYHA function class and LV EF in chronic heart failure patients (36). In an experimental model, ox-LDL induced ventricular myocyte damage and abnormal electric activity (37). Interestingly, in our study plasma ox-LDL before pPCI had the strongest correlation with the marker of infarct size and the parameters of heart failure, suggesting that the concentration of circulating ox-LDL particle before pPCI might impact the success of myocardial reperfusion and functional left ventricular recovery. Indeed, in experimental models of myocardial ischaemia-reperfusion, receptors for ox-LDL particles (lecithin-like ox-LDL receptors) were found to be up-regulated and coupled with apoptosis, necrosis and left ventricular functional deterioration (38).

hs-CRP is one of the most often evaluated biomarkers of atherosclerosis, since atherosclerosis is a process of low grade inflammation. It was shown to be increased in pre-diabetes (39, 40). However, this is the first study that showed that in the acute STEMI patients with pre-diabetes also have higher hs-CRP compared to non-diabetics while the difference compared to diabetics is insignificant. Pre-DM or DM were determinants of hs-CRP concentration on admission and on the 2nd day in univariate, but not in multivariate analyses.

The kinetics of serum hs-CRP in STEMI patients with the peak achieved 48 h to 72 h after mechanical revascularization, and decrement between the third and seventh day found in this study is similar to the results of others (43). Association between peak TnI and hs-CRP concentrations on day 2 and 7 found in this study is in accordance with the results from previous studies (41) suggesting that after mechanical revascularization hs-CRP increases in the first days proportionally to the infarct size. Clinical relevance of increased hs-CRP in STEMI patients treated with pPCI was extensively studied, and hs-CRP on admission, before or immediately after procedures was found to be a predictor of mortality (42–44) although its prognostic value depends on the time from chest pain onset to blood sampling. In the current study, 2nd day hs-CRP concentration in STEMI patients after pPCI significantly correlated with heart failure parameters, including Killip class, NT-pro BNP and left ventricular ejection fraction. The association between the baseline hs-C-reactive protein concentration and heart failure was previously described in a wide heterogeneous group of patients with the acute coronary syndrome (45).

Study limitation

The results of the current study should be interpreted with some limitation. The present study is a relatively small single centre study. However, our population consisted of homogenous first anterior STEMI patients treated by pPCI that allows more uniform dynamics of biomarkers.

Conclusion

Among patients with the first anterior STEMI treated by pPCI, there are significant differences in the concentration of hs-CRP and ox-LDL between pre-diabetics, diabetics and non-diabetic individuals. Diabetes is an important independent determinant of high ox-LDL in the acute STEMI. Both ox-LDL and hs-CRP levels in patients with acute STEMI treated by pPCI are associated with markers of acute heart failure. Whether the higher levels of ox-LDL and hs-CRP in pre-DM and DM STEMI patients could be translated into poor clinical outcome regarding heart failure remains to be determined in larger prospective studies.

Conflict of interest statement

The authors stated that have no conflicts of interest regarding the publication of this article.

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