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Inflammation markers are associated with metabolic syndrome and ventricular arrhythmia in patients with coronary artery disease*

Związek markerów zapalenia z zespołem metabolicznym i arytmią komorową u pacjentów z chorobą wieńcową

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Inflammation plays a major role in the development and progression of atherosclerosis and coronary artery disease (CAD). Inflammation markers, including white blood cell (WBC) count, C-reactive protein (CRP) and interleukin-6 (IL-6), are widely used for cardiovascular risk prediction.

The aim of the study was to establish factors associated with WBC, CRP and IL-6 in patients with CAD. Two functional polymorphisms in genes encoding enzymes participating in adenosine metabolism were analyzed (C34T *AMPD1*, G22A *ADA*).

Methods: Plasma concentrations of IL-6 were measured using high-sensitivity ELISA kits, and the nephelometric method was used for high-sensitivity CRP (hs-CRP) measurement in 167 CAD patients.

Results: Presence of metabolic syndrome (MS) and its components, presence of heart failure, severity of CAD symptoms, severe past ventricular arrhythmia (sustained ventricular tachycardia [sVT] or ventricular fibrillation [VF]), lower left ventricle ejection fraction, higher left ventricle mass index, higher end-diastolic volume and higher number of smoking pack-years were significantly associated with higher WBC, CRP and IL-6. Strong associations with arrhythmia were observed for IL-6 (median 3.90 vs 1.89 pg/mL, $p<0.00001$) and CRP concentration (6.32 vs 1.47 mg/L, $p=0.00009$), while MS was associated most strongly with IL-6. CRP and IL-6 were independent markers discriminating patients with sVT or VF. There were no associations between *AMPD1* or *ADA* genotypes and inflammation markers.

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Conclusions: WBC, CRP and IL-6 are strongly associated with components of the metabolic syndrome. Their strong association with life-threatening ventricular arrhythmia emphasizes the proarrhythmic role of inflammation in the increased cardiovascular risk of CAD patients.

Słowa kluczowe: **adenosine deaminase • AMP deaminase • C-reactive protein • genetic polymorphism • heart failure • interleukin-6**

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Introduction

Coronary artery disease (CAD) is one of the leading causes of both morbidity and mortality in the industrialized world. Recent studies indicated that environmental exposures, lifestyle factors, genetic determinants and inflammatory processes play an important role in the pathogenesis of CAD [19, 20]. Metabolic syndrome (MS), a constellation of CAD risk factors, includes atherogenic dyslipidemia, hypertension, abdominal obesity, hyperglycemia and insulin resistance, but it is also regarded as a proinflammatory state [18,24].

Inflammation plays a major role in the development and progression of atherosclerosis, implicating the logical candidacy of inflammatory cytokines for cardiovascular risk prediction [29]. Multiple potential biomarkers of atherosclerosis have been evaluated for their CAD predictive value. Such mediators can be derived from the interplay between obesity, inflammation, diabetes (DM) and CAD [38]. Obesity is currently considered as a constant state of low-grade inflammation that provides a direct link with atherosclerosis. Inflammation in obesity results from an altered secretion of mediators, such as adipokines and cytokines, by the increased adipose tissue mass [14]. These mediators also give rise to the development of DM and MS by inducing insulin resistance, hypertension and dyslipidemia, thus contributing to the proinflammatory milieu that enables the progression of atherosclerosis and development of CAD [45]. The progression of atherosclerosis is controlled by the balance between inflammatory mediators such as interleukin-6 (IL-6), C-reactive protein (CRP), interleukin-1 (IL-1), tumor necrosis factor (TNF), and anti-inflammatory mediators such as adenosine. Clinical observations showed that the increased inflammatory response correlated with the generation and perpetuation of supraventricular and ventricular arrhythmias [40].

IL-6 is a pleiotropic cytokine with both pro-inflammatory and anti-inflammatory properties. It is produced not only by immune cells and immune accessory cells, including monocytes and macrophages, but also by adipocytes and cardiovascular system components, such as endothelial cells, vascular smooth muscle cells, and ischemic cardiomyocytes [32]. It stimulates the synthesis of several acute-phase reaction proteins, such as CRP, serum amyloid A, and fibrinogen [28].

IL-1 is a proinflammatory cytokine, a mediator of the acute phase of inflammation by induction of local and systemic responses. IL-1 induces the expression of adhesion molecules on endothelial cells, which are required for the infiltration of the stressed tissue by inflammatory and immunocompetent cells [9,22]. Expression of IL-1s and their receptors has been demonstrated in atheromatous tissue, and serum levels of IL-1-cytokines have been correlated with various aspects of cardiovascular disease and their outcome. In vitro studies have confirmed the pro-atherogenic properties of IL-1alpha and IL-1beta, such as up-regulation of endothelial adhesion molecules, activation of macrophages and smooth muscle cell proliferation [4]. The role of the IL-1 signaling pathway in advanced atherosclerosis is complex.

CRP is a systemic marker of inflammation produced by the liver. Previous reports indicated the relationship between CRP, MS and cardiovascular events [46,51]. CRP may promote atherosclerosis by reducing endothelial nitric oxide synthase (eNOS) expression, mediating the negative effects of oxidized low-density lipoprotein (LDL) on endothelial cells such as expression of adhesion molecules. Moreover, CRP is involved in activation of the complement cascade and promotes foam cell formation [3,15].

The relationship between white blood cell (WBC) count and CAD was suggested by numerous studies, which

indicated that it can be used to predict the incidence of coronary events [44], and high WBC count is associated with increased mortality rates in patients who present with acute coronary syndromes [12]. It is consistent with the current paradigm of the inflammatory origin of atherosclerosis. Leukocytes play a key role in the initiation and progression of the disease by releasing cytokines and bringing about further macrophage recruitment and the proliferation of smooth muscle cells within the vascular wall. In addition, protease secretion leads to endothelial damage of the coronary vessels, exposing thrombogenic collagen and predisposing the vessels to thrombus formation [8]. The association between WBC count and CAD has been consistently observed in different populations and appears to be independent of other traditional coronary risk factors [5]. High WBC count is a strong and independent predictor of coronary risk in subjects with and without coronary heart disease [37].

The aim of the study was to establish clinical and biochemical factors associated with commonly used markers of inflammation – blood WBC and plasma concentrations of CRP, IL6 and IL1β – in patients with coronary artery disease (CAD). Since adenosine exerts anti-inflammatory effects, two common functional polymorphisms in genes encoding enzymes participating in adenosine metabolism, i.e. AMP deaminase-1 (*AMPD1*, C34T, Gln12Stop) and adenosine deaminase (*ADA*, G22A, Asp8Asn, ADA*1/*2), were included in the analysis.

Material and methods

One hundred sixty-seven patients with CAD (aged 59±8 years, 80% men), Caucasian Polish residents treated at the Department of Cardiology of Pomeranian Medical University, were studied. The same study group was described in our previous study [48]. CAD was diagnosed in all of them on the basis of the presence of at least one coronary lesion in coronary angiography (≥40% diameter stenosis of the left main coronary artery or ≥50% stenosis of one of the three major epicardial arteries or ≥70% stenosis of a branch). They were clinically stable with optimal pharmacological treatment and no acute coronary syndromes, heart failure exacerbations, or revascularization procedures within one month before enrolment. Patients with hemodynamically significant congenital or acquired valve diseases, advanced renal failure (serum creatinine >2.5 mg/dL), malignant neoplasms, rheumatoid arthritis, or other autoimmune connective tissue diseases were excluded from the study. The investigation conformed to the principles outlined in the Declaration of Helsinki and was approved by the institutional ethics committee. Informed consent was obtained from each patient.

Heart failure was evidenced in 70 patients (42%) by clinical symptoms, echocardiography, and brain natriuretic peptide (BNP) plasma concentration. Implantable cardioverter-defibrillators (ICD) had been implanted previously in 34 patients (20%) according to clinical guidelines. Past arrhythmia episodes were evidenced on the basis of patient documentation, including standard ECG, Holter monitoring and ICD recordings. Basic morphometric parameters were measured in each patient. Echocardiography was performed in all patients by one experienced cardiologist. The clinical and laboratory characteristics of the study group are presented in Table 1.

Table 1. Characteristics of the study group (n=167)

Parameter	Value
Gender	133 M / 34 F (80%/20%)
Age [years]	59.2 ± 8.4 {58 (13)}
Number of main coronary arteries with lesions	2.3 ± 1.0 {2 (2)}
Past myocardial infarct	129 (77%)
Heart failure	70 (42%)
Implantable cardioverter-defibrillator (ICD)	34 (20%)
Atrial fibrillation (paroxysmal or continuous)	9 (5%)
Sustained ventricular tachycardia (sVT) episode	13 (8%)
Ventricular fibrillation (VF) episode	17 (10%)
Hypertension	64 (38%)
Systolic blood pressure [mmHg]	135 ± 20 {130 (30)}
Diastolic blood pressure [mmHg]	83 ± 11 {80 (10)}
Diabetes type 2	31 (19%)
Fasting plasma glucose [mg/dL]	114 ± 32 {104 (25)}
Current smoking	24 (14%)
Asthma or chronic obstructive pulmonary disease	11 (7%)
Metabolic syndrome (ATP III)	71(43%)
Metabolic syndrome (IDF)	91 (54%)
Body mass index (BMI) [kg/m^2]	28.1 ± 4.1 {27.4 (5.8)}
Left ventricle ejection fraction (LVEF) [%]	47.2 ± 16.1 {49 (26)}
Left ventricle end-diastolic diameter (LVEDD) [mm]	57.7 ± 9.8 {56 (13)}
Left ventricle mass index (LVMI) [g/m^2]	148 ± 39 {140 (50)}
Plasma B-type natriuretic peptide (BNP) [pmol/L]	231 ± 359 {115 (205)}
Glomerular filtration rate (GFR_{MDRD}) [mL/min/1.73 m^2]	70.5 ± 12.7 {71.3 (16.9)}
Blood haemoglobin [mmol/L]	8.61 ± 0.69 {8.62 (0.80)}
Statin therapy	153 (92%)
Serum total cholesterol [mg/dL]	190.8 ± 38.5 {185 (51)}
Serum HDL cholesterol [mg/dL]	53.3 ± 15.2 {51 (19)}
Serum LDL cholesterol [mg/dL]	103.0 ± 29.5 {100 (34)}
Serum triacylglycerols [mg/dL]	127.1 ± 81.7 {110 (78)}

Data are presented as mean ± SD {median (interquartile range)} or number (percent).

Table 2. Correlations of white blood cells count (WBC), plasma CRP and IL-6 concentrations with quantitative variables (Spearman rank correlation coefficients)

Correlated parameters	WBC	CRP	IL-6
Age	-0.15 ^	-0.15 *	+0.02
Severity of coronary artery disease symptoms (CCS class)	+0.17 *	+0.17 *	+0.20 **
Severity of heart failure symptoms (NYHA class)	+0.28 ***	+0.17 *	+0.35 ***
Number of main coronary arteries with lesions	-0.10	-0.06	+0.12
Systolic blood pressure	-0.07	-0.15 ^	-0.01
Diastolic blood pressure	-0.01	-0.01	+0.07
Heart rate	+0.03	+0.17 *	+0.12
ECG ST segment maximal depression (n=161)	+0.18 *	+0.11	+0.30 ***
Left ventricle ejection fraction (LVEF)	-0.29 ***	-0.16 *	-0.29 ***
Left ventricle shortening fraction (LVSF)	-0.28 ***	-0.18 *	-0.31 ***
Left ventricle end-diastolic diameter (LVEDD)	+0.18 *	+0.08	+0.24 **
Left ventricle end-diastolic diameter (LVESD)	+0.25 **	+0.13	+0.28 ***
Left ventricle mass index (LVMI)	+0.22 **	+0.17 *	+0.26 ***
Left ventricle end-diastolic volume (LVEDV)	+0.29 ***	+0.18 *	+0.24 **
Plasma B-type natriuretic peptide (BNP)	+0.04	+0.04	+0.19 *
Serum creatinine	+0.17 *	+0.13	+0.20 *
Glomerular filtration rate (GFR_{MDRD})	-0.02	-0.09	-0.16 *
BMI	+0.17 *	+0.31 ***	+0.30 ***
Waist circumference	+0.30 ***	+0.31 ***	+0.32 ***
Waist-to-hip ratio	+0.30 ***	+0.25 ***	+0.32 ***
Smoking pack years	+0.22 **	+0.24 **	+0.20 *
Fasting serum glucose	+0.22 **	+0.24 **	+0.30 ***
Blood haemoglobin	+0.27 ***	+0.09	+0.09
Total cholesterol	+0.29 ***	+0.25 **	+0.23 **
HDL cholesterol	-0.26 ***	-0.27 ***	-0.26 ***
LDL cholesterol	+0.35 ***	+0.34 ***	+0.31 ***
Triacylglycerols	+0.31 ***	+0.25 **	+0.34 ***
Number of metabolic syndrome components (ATP III)	+0.32 ***	+0.33 ***	+0.44 ***

^ $p<0.06$, * $p<0.05$, ** $p<0.01$, *** $p<0.001$

Blood samples were taken from the patients without infections or other acute inflammatory diseases in a fasting state into tubes containing EDTA. One tube was subjected to standard automated blood count analysis (Cell-Dyn 3700 SL, Abbott) including WBC and hemoglobin. Another tube was immediately cooled and centrifuged and the plasma was frozen at -80°C. Plasma CRP concentration was measured with the high-sensitivity (limit of quantitation: 0.175 mg/L) immunonephelometric method using the CardioPhase hs-CRP test and a BN 100 nephelometer (Dade Behring). Plasma IL-6 and IL1β concentrations were measured with R&D ELISA high-sensitivity Quantikine kits (HS600B and HSLB00C, respectively) with limits of detection 0.04 and 0.06 pg/mL, respectively. Plasma B-type natriuretic peptide (BNP) concentration was measured with the AxSym assay (Abbott). Serum concentrations of glucose, total, LDL and high-density lipoprotein (HDL) cholesterol, triacylglycerols and creatinine were measured with standard automated methods. Renal function was assessed on the basis of glomerular filtration rate (GFR) estimated by the simplified Modification of Diet in Renal Disease (MDRD) formula using serum creatinine concentration. Metabolic syndrome was diagnosed on the basis of National Cholesterol Education Program (NCEP) ATP III (2001) [25] or International Diabetes Federation (IDF) (2006) criteria [31].

DNA was isolated from EDTA-anticoagulated blood. Previously described PCR-RFLP methods were used for *ADA* [49] and *AMPD1* [47] genotyping.

Quantitative variables were presented as mean ± SD or median (interquartile range – IQR). The Spearman rank

Table 3. Associations of white blood cells count (WBC, G/L), plasma CRP (mg/L) and IL-6 (pg/mL) concentrations with qualitative variables presented as median (interquartile range)

Parameter	Value	N	WBC	CRP	IL-6
Gender	Male	133	6.30 (2.15)	1.62 (3.27)	2.13 (2.47)
	Female	34	5.80 (2.67)	1.50 (3.34)	1.99 (1.62)
Heart failure	Present	70	6.87 (2.32) ***	2.05 (4.86) *	3.04 (3.24) ***
	Absent	97	5.68 (2.33)	1.44 (2.4)	1.70 (1.69)
Past myocardial infarction	Present	129	6.49 (2.02) *	1.66 (3.35)	2.41 (2.28) *
	Absent	38	5.57 (2.39)	1.27 (2.54)	1.61 (1.45)
Current smoking	Yes	24	7.18 (2.18) **	1.70 (4.75)	2.81 (2.6)
	No	143	6.10 (2.24)	1.51 (3.19)	2.03 (2.4)
Hypertension	Present	103	6.3 (2.35)	1.78 (3.73)	2.29 (2.59)
	Absent	64	6.17 (2.31)	1.41 (2.22)	1.91 (1.89)
Diabetes (type 2)	Present	31	7.01 (2.15) **	2.22 (6.03) ^	3.28 (3.64) ***
	Absent	136	6.00 (2.26)	1.49 (2.67)	1.91 (2.12)
Obesity (BMI > 30 kg/m^2)	Present	51	6.62 (2.14)	3.25 (5.89) ***	2.97 (4.20) ***
	Absent	116	6.04 (2.30)	1.34 (2.25)	1.90 (2.05)
High waist (ATP III)	Present	64	6.67 (1.84) ^	2.24 (5.63) **	2.73 (3.24) ***
	Absent	103	5.8 (2.33)	1.34 (2.34)	1.75 (2.33)
Metabolic syndrome (ATP III)	Present	71	6.86 (1.86) ***	2.26 (6.08) ***	3.12 (3.6) ***
	Absent	96	5.6 (2.43)	1.29 (1.86)	1.66 (1.63)
High waist (IDF)	Present	112	6.57 (2.23) **	2.06 (3.65) **	2.37 (2.46) *
	Absent	55	5.38 (2.00)	1.23 (1.32)	1.61 (2.55)
Metabolic syndrome (IDF)	Present	91	6.62 (2.09) **	2.12 (4.05) **	2.42 (2.94) **
	Absent	76	5.64 (2.39)	1.23 (1.55)	1.78 (2.38)
AF paroxysmal or continuous	Present	9	6.29 (1.42)	1.83 (11.27)	2.47 (2.11)
	Absent	158	6.22 (2.33)	1.56 (3.27)	2.04 (2.4)
Sustained ventricular tachycardia (sVT)	Present	13	7.11 (1.09) **	11.5 (10.21) ***	4.15 (2.95) ***
	Absent	154	6.1 (2.34)	1.49 (2.63)	1.92 (2.29)
Ventricular fibrillation (VF)	Present	17	7.32 (1.79) **	5.08 (12.1) **	3.65 (2.58) **
	Absent	150	6.1 (2.26)	1.51 (2.6)	1.97 (2.18)
sVT or VF	Present	26	7.26 (1.7) ***	6.32 (13.39) ***	3.90 (3.38) ***
	Absent	141	5.98 (2.19)	1.47 (2.36)	1.89 (1.84)
Implanted ICD	Present	34	7.11 (1.72) ***	5.22 (12.58) ***	4.09 (3.44) ***
	Absent	133	5.9 (2.25)	1.29 (2.04)	1.89 (1.76)
AMPD1 C34T genotype	CT+TT[a]	48	5.84 (3.07)	1.49 (3.27)	1.89 (2.52)
	CC	119	6.3 (2.17)	1.62 (3.29)	2.33 (2.34)
ADA G22A genotype[b]	GA	10	5.57 (2.77)	1.16 (3.4)	1.45 (1.43)
	GG	157	6.23 (2.18)	1.62 (3.2)	2.26 (2.34)

^ $p<0.06$, * $p<0.05$, ** $p<0.01$, *** $p<0.001$ for difference between the groups with indicated parameter values

[a] there were 41 patients with CT and 7 with TT genotype

[b] there were no patients with AA genotype

correlation coefficient (Rs) and the Mann-Whitney test were used for univariate statistical analysis. Multiple linear regression and logistic regression were used for multivariate analysis after logarithmic transformation of CRP and IL-6 concentration values. The standardized beta regression coefficients were calculated to compare the relative effect of each independent variable on the prognosis of the values of quantitative dependent vari-

ables. Independent variables were selected with the "best subset" method to obtain a significant association for each variable in the model, and after additional adjustment for age and gender. Some continuous and rank variables were transformed to dichotomous ones using cut-off values selected according to the ATP III or IDF MS definition (waist circumference, triacylglycerols) or empirically to obtain best fit (HDL cholesterol, LDL cholesterol, CCS class). Associations with $p<0.05$ were considered statistically significant, while a p-value <0.06 was interpreted as borderline significant. The analyses were performed with Statistica 10 software.

Results

In the whole study group WBC was 6.34 ± 1.74 (median 6.23 [IQR 2.32]) G/L and plasma concentrations were 5.2 ± 12.6 (1.6 [3.3]) mg/L for CRP and 4.19 ± 7.09 (2.08 [2.43]) pg/mL for IL-6. WBC was positively correlated with CRP (Rs=+0.46, $p<0.00001$) and IL-6 (Rs=+0.47, $p<0.00001$). The correlation between CRP and IL-6 was stronger (Rs=+0.57, $p<0.00001$).

Pilot studies for the analysis of IL-1β were performed with 51 random patient plasma samples. In most cases IL-1β concentrations were very low (< 1 pg/mL). Further experiments with sample dilution and the use of another anticoagulant (heparin) showed that the results are inconsistent and unknown interfering plasma compounds are responsible for overestimation of the concentration in some samples. We concluded that in spite of the fact that the Quantikine HS kit was designed to measure low IL-1β concentrations in plasma, its sensitivity and specificity are not sufficient with respect to patients with cardiovascular diseases, in whom autoimmune diseases were excluded. This is consistent with the statement of the manufacturer that IL-1β is detectable only in 2-25% of healthy volunteers, depending on the anticoagulant used. Therefore, finally we decided to give up further analysis and presentation of IL-1β plasma concentrations in our study group.

In the univariate analysis (Tables 2 and 3) the common factors significantly (or with borderline significance) associated with higher WBC, CRP and IL-6 were:

- presence of MS (according to both ATP III and IDF definitions), its components (diabetes, high waist circumference, LDL cholesterol, triacylglycerols, fasting glucose, low HDL cholesterol) and other morphometric and biochemical parameters related to MS (high waist-to-hip ratio, BMI, total cholesterol),
- presence of more advanced or complicated CAD including presence of heart failure (and higher NYHA class), severity of coronary artery disease symptoms (higher CCS class), severe past ventricular arrhythmia (including sustained ventricular tachycardia [sVT] and ventricular fibrillation [VF]), lower left ventricle ejection or shortening fraction (LVEF, LVSF), higher left ventricle mass index (LVMI) and left ventricle end-diastolic volume (LVEDV),
- higher number of smoking pack-years.

Higher WBC and IL-6 (but not CRP) were also associated with higher left ventricle end-diastolic (LVEDD) and end-systolic (LVESD) diameters, greater ST segment maximal depression in ECG, higher serum creatinine and presence of past myocardial infarction. As regards parameters associated significantly with only one inflammation marker, WBC correlated positively with higher blood hemoglobin and current smoking, CRP correlated positively with heart rate and negatively with age, and IL-6 correlated positively with plasma BNP and negatively with glomerular filtration rate.

The strongest correlation (Rs=+0.44, $p<0.000001$) was observed between IL-6 and the number of MS components according to ATP III (Table 2). Particularly high statistical significance was obtained for differences between patients with and without sVT or VF in IL6 (medians 3.90 vs 1.89 pg/mL, $p<0.00001$) and CRP concentrations (6.32 vs 1.47 mg/L, $p=0.00009$).

In the multivariate analyses (Tables 4, 5 and 6), past sVT or a VF episode was a common independent predictor of higher IL-6, CRP and WBC. Other independent predictors of higher levels of inflammation markers were: presence of heart failure (IL-6 and WBC), more severe CAD symptoms (IL-6 and CRP), various indices of obesity (ATP III criteria for IL-6, IDF criteria for WBC, BMI for CRP), lower HDL cholesterol (IL-6 and CRP), higher LDL cholesterol (CRP and WBC), higher triacylglycerols (IL-6 and WBC) and current smoking (only WBC). Additional adjustment for patients' age and gender did not change the coefficients of the multivariate models significantly.

There were no associations between *AMPD1* C34T or *ADA* G22A genotypes and inflammation markers in the univariate analysis. However, presence of the *AMPD1* 34T mutated allele was associated with higher CRP concentration (β=+0.16, 95%CI=0.02-0.29, $p=0.020$ for CT+TT vs. CC genotypes) when it was added to the multivariate model presented in Table 5.

Strong associations between sVT or VF and all studied inflammation markers prompted us to check whether they are useful for the discrimination of patients with severe ventricular arrhythmia. Multivariate logistic regression analysis with past sVT or VF as the dependent variable showed that only higher LVEDV and higher level of any of the inflammation markers were significant discriminators of past ventricular arrhythmia episodes. The association was most significant for CRP logarithm (OR=2.13, 95%CI=1.45-3.13, $p=0.00011$), slightly less significant for IL-6 logarithm (OR=2.51, 95%CI=1.51-4.17, $p=0.00036$), and least significant for WBC (OR=1.51, 95%CI=1.14-2.00, $p=0.0018$). The power for discrimination of patients with sVT or VF, which

Table 4. Multiple linear regression model for logarithm of IL-6 plasma concentration as the dependent variable (R^2=0.36)

Independent variables	Beta coefficient (95% CI)	p-value
Presence of heart failure	+0.19 (+0.06 – +0.32)	0.0052
CCS class > 2 (more than slight limitation of ordinary activity)	+0.19 (+0.06 – +0.32)	0.0039
Past sVT or VF episode	+0.24 (+0.11 – +0.37)	0.00033
Waist ≥ 102 cm (males) or ≥ 88 cm (females) [a]	+0.17 (+0.04 – +0.30)	0.0087
HDL cholesterol ≥ 68 mg/dL	-0.18 (-0.31 – -0.05)	0.0060
Triacylglycerols ≥ 150 mg/dL	+0.24 (+0.11 – +0.37)	0.00045

[a] obesity according to ATP III criteria

Table 5. Multiple linear regression model for logarithm of CRP plasma concentration as the dependent variable (R^2=0.33)

Independent variables	Beta coefficient (95% CI)	p-value
CCS class ≥ 2 (at least slight limitation of ordinary activity)	+0.20 (+0.07 – +0.33)	0.0021
Past sVT or VF episode	+0.26 (+0.13 – +0.39)	0.00012
BMI [kg/m^2]	+0.27 (+0.14 – +0.40)	0.00006
HDL cholesterol [mg/dL]	-0.23 (-0.36 – -0.10)	0.00049
LDL cholesterol [mg/dL]	+0.20 (+0.07 – +0.33)	0.0022

Table 6. Multiple linear regression model for logarithm of blood WBC as the dependent variable (R^2=0.34)

Independent variables	Beta coefficient (95% CI)	p-value
Presence of heart failure	+0.22 (+0.09 – +0.35)	0.0011
CCS class > 2 (more than slight limitation of ordinary activity)	+0.16 (+0.02 – +0.29)	0.020
Past sVT or VF episode	+0.18 (+0.05 – +0.32)	0.0070
Waist ≥ 94 cm (males) or ≥ 80 cm (females) [a]	+0.16 (+0.02 – +0.29)	0.020
Ln (Triacylglycerols [mg/dL]) [b]	+0.22 (+0.08 – +0.35)	0.0016
LDL cholesterol [mg/dL]	+0.14 (+0.01 – +0.28)	0.041
Current smoking	+0.20 (+0.07 – +0.33)	0.0028

[a] obesity according to IDF criteria
[b] transformed logarithmically

Table 7. Univariate and multivariate logistic regression for logarithm of CRP plasma concentration and other clinical parameters discriminating patients with past sVT or VF episode

Analysis	Univariate			Multivariate	
Independent variables	OR (95% CI)	p	ROC AUC [a]	OR (95% CI)	p-value
Ln (CRP [mg/L])	2.034 (1.433–2.887)	0.00006	0.736	2.095 (1.412–3.110)	0.00022
LVEDV [mL]	1.012 (1.006–1.019)	0.00012	0.731	1.013 (1.006–1.020)	0.00036
LDL cholesterol > 140 mg/dL	2.878 (1.040–7.969)	0.040	0.583 [b]	3.225 (0.997–10.428)	0.049

[a] area under receiver operating characteristic (ROC) curve
[b] for LDL cholesterol as quantitative variable

was assessed as the area under the receiver operating characteristic (ROC) curve, was similar for CRP (0.736, 95%CI: 0.620-0.851), IL-6 (0.766, 95%CI: 0.654-0.878), WBC (0.737, 95%CI: 0.621-0.852) and LVEDV (0.731, 95%CI: 0.615-0.847). Only in the model containing CRP, LDL cholesterol > 140 mg/dL was an additional significant marker of higher risk (Table 7). No other analyzed variables were significant independent factors discriminating patients with past sVT or VF.

Discussion

In this study we examined the association between WBC, CRP and IL-6 plasma concentrations and clinical and biochemical parameters in patients with CAD. Many reports have been published on associations between inflammation markers and cardiovascular diseases. Therefore we did not aim to confirm that inflammation is a significant risk factor of CAD, but to explore associations between inflammation and other features (including metabolic syndrome and arrhythmia) in patients already diagnosed with CAD.

IL-1beta plasma concentrations were too low for reliable measurement in our patients. Increased levels of WBC, CRP and IL-6 were associated with heart failure, severity of CAD symptoms, severe past ventricular arrhythmia, lower left ventricle ejection fraction, higher left ventricle mass index or end-diastolic volume, metabolic syndrome components and higher number of smoking pack-years. In multivariate analyses the common independent predictors of higher WBC, CRP and IL-6 were: symptoms of advanced CAD, ventricular arrhythmia, obesity and dyslipidaemia.

The relatively high proportion of patients with heart failure or an implanted ICD and severe ventricular arrhythmias in the study group reflects the profile of the Department of Cardiology, which is an academic tertiary referral centre.

Advanced CAD symptoms (reflected by higher CCS class) and presence of heart failure, as a result of functional heart damage related to ischemia, were independent predictors of higher levels of inflammation markers. Interestingly, echocardiography parameters were not significant predictors of inflammation markers in multivariate models including clinical symptoms. This association may indicate that the markers reflect the increasing intensity of inflammation during the natural clinical course of progressing CAD. It would be very interesting to investigate in prospective studies whether coronary revascularization, which alleviates CAD symptoms and improves cardiovascular outcome, results in a concomitant decrease of inflammation markers.

The present results confirm the strong association of inflammation with metabolic syndrome components in CAD patients. The MS components, including obesity, low HDL cholesterol, high triacylglycerols, as well as high LDL cholesterol, were independent predictors of higher levels of inflammation markers. Other MS components lost significance in multivariate analysis (diabetes or hyperglycemia) or were not associated with inflammation (hypertension). Obesity and dyslipidaemia are known risk factors for adverse cardiovascular events. An association of metabolic syndrome with elevated markers of inflammation is evident in many studies, but the responsible mechanisms are not fully understood [54]. It seems that the proinflammatory state of obesity and metabolic syndrome induces insulin resistance, leading to clinical and biochemical manifestations of the metabolic syndrome [18].

Several prospective studies have established that IL-6 levels are increased in subjects with obesity or MS and that raised IL-6 levels are predictive for the development of MS and DM [30]. Furthermore, in the liver, IL-6 contributes to insulin resistance by impairment of insulin signaling, which leads to decreased levels of glycogen synthase and decreased glucose uptake [57]. By contrast, in skeletal muscle IL-6 is secreted in response to exercise and increases glucose uptake [43]. IL-6 induces the secretion of CRP, especially during an acute-phase response to inflammation or tissue injury [36]. The elevated CRP levels observed in subjects with abdominal obesity and MS are caused by IL-6 released from macrophages in the visceral adipose tissue and subendothelial space, which stimulates CRP secretion from the liver. CRP contributes to insulin resistance by attenuating insulin signaling [17]. Previous studies have confirmed that elevated CRP levels are predictive of the development of insulin resistance, DM and MS [46,51]. It was observed that CRP levels and WBC count were strongly related to components of the insulin resistance syndrome, such as BMI, waist circumference, insulin sensitivity, fasting insulin and proinsulin [26].

Elevated WBC levels have been associated with elevated serum triglyceride and cholesterol levels, fasting glucose levels, and diastolic blood pressure [13]. Leukocytosis is also associated with several disorders that characterize the metabolic syndrome and with micro- and macrovascular complications in patients with diabetes [41,42,56].

The association of *AMPD1* 34T allele with higher CRP observed in multivariate analysis should be treated with extreme caution, since it was not observed in the univariate analysis and it lost significance when BMI, LDL or HDL cholesterol was excluded from the multivariate model. Lack of a univariate association between C34T genotype and CRP in patients with past myocardial infarction was reported previously [1]. The multivariate relation observed in our study is not consistent with potential anti-inflammatory action of higher adenosine concentrations in 34T carriers [16]. This phenomenon may be related to the association between metabolic syndrome and C34T polymorphism. In our previous study we found that the polymorphism is associated with a reduced frequency of obesity in CAD patients and

of hyperglycemia and diabetes in both CAD and heart failure patients [47]. Taken together, these results suggest that intercorrelations between inflammation, metabolic syndrome and the common functional *AMPD1* polymorphism need further research.

Our study revealed a strong association of the inflammation markers, particularly IL-6 and CRP, with past severe ventricular arrhythmia episodes. The strength of the association was similar to that of LVEDV, which is a potent marker of structural heart damage, with a proven prognostic role for the risk of cardiovascular events [21], and these factors were independent of each other in the multivariate model.

Many previous studies have suggested that the inflammatory process plays an important role in generation of cardiac arrhythmia, but the majority of these reports concerned atrial fibrillation (AF) [28]. These findings are supported by experimental studies, since atrial biopsies taken from patients with AF compared with controls have demonstrated evidence of inflammatory infiltrates and oxidative damage within the atrial tissue [10]. Inflammation and oxidative injury directly affect atrial myocyte contraction, electrical conduction, myocyte apoptosis, and cardiac fibrosis [39]. CRP can induce AF, causing the disarray of normal cell membrane structure by interaction with lysophospholipids followed by activation of the complement system and phagocytosis [35]. Our results did not show an association of AF with inflammation markers, but there were only 9 patients with AF in our study group.

Similar mechanisms may be involved in the generation of ventricular arrhythmia. Moreover, inflammatory biomarkers can transform a stable atherosclerotic plaque into an unstable lesion, leading to ischemia-induced ventricular arrhythmias and sudden cardiac death events [40]. In the study of Albert *et al*., higher CRP levels were independently associated with an increased risk of sudden cardiac death over a 17-year follow-up period [2]. In another study, frequent premature ventricular contractions together with high CRP were associated with higher risk of death and acute myocardial infarction [50]. High peak serum CRP was an independent predictor of VT/VF in STEMI patients treated with primary percutaneous coronary intervention, while WBC was also significantly higher in patients with VT/VF [33]. High serum CRP was an independent predictor of VT/VF or cardiac death after ICD implantation [58]. In another study, increased CRP was an independent predictor of VT in ICD recipients after myocardial infarction [7]. Elevated preimplantation hs-CRP serum level was independently associated with increased risk for appropriate ICD therapy [55]. A possible mechanism of the associations is suggested by histological studies which demonstrated a positive correlation between CRP and the number of thin cap coronary atheromas [11]. CRP may also have direct arrhythmogenic properties by locally activating complement and inducing oxidative stress and apoptosis [40]. Flevari et al. [27] observed higher IL-6 concentration in patients with malignant ventricular arrhythmias, and there was a positive correlation between the number of arrhythmic episodes and IL-6. VF survivors compared to those without VF during acute MI had higher circulating levels of IL-6 [23]. Increased serum IL-6 was associated with an increased incidence of ventricular tachyarrhythmias in ICD recipients with CAD or idiopathic dilated cardiomyopathy [52]. Electrical storm defined as 3 separate VT/VF events in ICD patients with structural heart disease was associated with significantly elevated IL-6 and hs-CRP serum concentrations [53]. However, another study [34] did not detect an association of IL-6 and CRP with ventricular tachyarrhythmias during 5.1 months of follow-up. Biasucci et al. reported that CRP >3 mg/L was not associated with sudden cardiac death or fast VT/VF, though it was a strong predictor of HF mortality in CAD patients with ejection fraction <30% and an implanted ICD [6].

The results of the current study suggest that inflammatory processes may be equally important as structural myocardium injury as a trigger of life-threatening arrhythmia events. Proper stratification of ventricular arrhythmia risk is very important for patients with CAD, since implantation of an ICD may prevent many arrhythmia-associated deaths. It seems that measurement of the level of an inflammation marker, such as IL-6 or CRP, might be an important component of such a risk stratification algorithm. Further prospective studies are needed to establish (and compare) their prognostic values.

One of the limitations of our study is its retrospective design – the arrhythmia episodes were recorded and patients received proper treatment (ICD implantation and/or antiarrhythmic drugs) before the measurement of inflammation markers. Although such treatment probably does not directly affect the markers, only a prospective study could confirm the role of the inflammation markers as strong independent predictors of sVT or VF.

Conclusions

Elevated levels of the inflammation markers WBC, CRP and IL-6 are associated with many proven cardiovascular risk factors, including components of the metabolic syndrome, in patients with coronary artery disease. Their strong association with life-threatening ventricular arrhythmia emphasizes the proarrhythmic role of inflammation in the increased cardiovascular risk of CAD patients.

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