Concentrations of vascular endothelial growth factor, C-reactive protein and interleukin 6 in patients qualified to surgical treatment of coronary artery disease

Stężenie czynnika wzrostu komórek śródbłonka, białka C-reaktywnego i interleukiny 6 u chorych zakwalifikowanych do leczenia operacyjnego choroby wieńcowej

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Abstract

Introduction: Atherosclerosis is a chronic inflammatory disease involving release in such biochemical markers as C-reactive protein (CRP) and interleukin 6 (IL-6). Attention was already given to pro-atherosclerotic role of vascular endothelial growth factor (VEGF). The study aimed to assess the concentrations of VEGF, CRP and IL-6 in patients qualified to surgical treatment of coronary artery disease and to correlate the values with lipids' concentrations.

Material and Methods: In a case-control study, we investigated 38 patients (aged 65.6 ±10.0) qualified to coronary artery bypass grafting (CABG) (study group), and 37 healthy volunteers (aged 24.3 ±7.6) as a control group. The control group consisted of healthy outpatients with proper lipids' concentrations, and negative history of pharmacological treatment or any heart disease.

Results: Study group subjects had higher CRP and VEGF concentrations compared to controls ($p < 0.05$) with no difference in IL-6 concentrations between groups. VEGF was positively correlated with total cholesterol ($R = 0.42$; $p = 0.03$) and LDL concentrations ($R = 0.48$; $p = 0.01$), and CRP was negatively correlated with HDL level ($R = –0.45$; $p = 0.02$). In the control group CRP was also negatively correlated with HDL concentration ($R = –0.88$; $p = 0.002$). After adjustment for potential confounders, CRP was associated with total cholesterol ($b = 0.64$; $p = 0.004$), HDL ($b = –1.25$; $p < 0.0001$) and triglyceride ($b = –0.25$; $p = 0.02$) concentrations, and VEGF was dependent only on LDL level ($b = 41.7$; $p = 0.05$).

Conclusions: Subjects qualified to CABG have higher CRP and VEGF concentrations compared to subjects without coronary artery disease. VEGF is positively correlated with total cholesterol and LDL concentrations, and CRP is negatively correlated with HDL and triglyceride concentrations.

Streszczenie

Wstęp: Miażdżyca jest chorobą przewlekłą o podłożu zapalnym, które jest identyfikowane pomiarem takich markerów, jak białko C-reaktywne (CRP) oraz interleukina 6 (IL-6). W powstawaniu miażdżycy coraz częściej opisywany jest także udział czynnika wzrostu komórek śródbłonka naczyń (VEGF). Celem pracy była ocena stężenia VEGF, CRP oraz IL-6 u chorych zakwalifikowanych do leczenia operacyjnego choroby niedokrwiennej serca oraz korelacja tych wartości ze stężeniami poszczególnych frakcji lipidów.

Materiał i metody: W projekcie o charakterze badania kliniczno-kontrolnego uczestniczyło 38 chorych w wieku 65,6 ±10,0 lat, zakwalifikowanych do pomostowania aortalno-wieńcowego (CABG) (grupa badana) oraz 37 zdrowych ochotników (w wieku 24,3 ±7,6 roku), którzy stanowili grupę kontrolną. U osób z grupy kontrolnej nigdy nie rozpoznano żadnej choroby serca i nie przyjmowały one żadnych leków.

Wyniki: Osoby z grupy badanej cechowały sie znamiennie statystycznie wyższymi wartościami CRP i VEGF niż osoby z grupy kontrolnej ($p < 0,05$), jednak nie stwierdzono różnicy dla IL-6. VEGF dodatnio korelowało ze stężeniem cholesterolu frakcji LDL ($R = 0,42$; $p = 0,03$), natomiast CRP było ujemnie skorelowane ze stężeniem HDL ($R = –0,45$; $p = 0,02$) u wszystkich badanych. W grupie kontrolnej CRP także było ujemnie skorelowane ze stężeniem HDL ($R = –0,88$; $p = 0,002$). Po uwzględnieniu wpływu czynników potencjalnie zakłócających obserwacje CRP zależało istotnie od stężenia całkowitego cholesterolu ($b = 0,64$; $p = 0,004$), HDL ($b = –1,25$; $p < 0,0001$) i triglicerydów ($b = –0,25$; $p = 0,02$), natomiast stężenie VEGF zależało jedynie od wartości LDL ($b = 41,7$; $p = 0,05$).

Wnioski: Pacjenci kwalifikowani do CABG charakteryzują się istotnie wyższymi wartościami CRP i VEGF w porównaniu z osobami nieobciążonymi chorobą niedokrwienną serca. Stężenie

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Key words: vascular endothelial growth factor, C-reactive protein, interleukin 6, coronary artery disease, coronary artery bypass grafting.

VEGF zależy od stężenia całkowitego cholesterolu i jego frakcji LDL, natomiast CRP jest ujemnie skorelowane ze stężeniem HDL oraz triglicerydów.

Słowa kluczowe: czynnik wzrostu komórek śródbłonka naczyń, białko C-reaktywne, interleukina 6, choroba niedokrwienna serca, pomostowanie aortalno-wieńcowe.

Introduction

Inflammation is confirmed to play a crucial role in the development of atherosclerosis, from its sub-clinical initiation through the progression at stage of chronic coronary artery disease, and complications of atherosclerosis, including acute coronary syndromes and sudden cardiac death [1]. In the light of recent data, atherosclerosis can be considered a chronic inflammatory disease which varies in its mechanisms, according to the stage of the disease [2]. The results of epidemiological studies revealed that the occurrence of atherosclerosis is strongly related to persistently high total plasma cholesterol, and specifically to LDL cholesterol concentrations, elevation of serum triglycerides, presence of small LDL particles and low HDL-cholesterol levels [3].

Due to its systemic inflammatory background resulting from oxidative stress, several biochemical markers have been found to correlate with the progression of atherosclerosis and predict the outcomes such as myocardial infarction, stroke or peripheral artery disease [2, 4]. These acknowledged markers of inflammation include C-reactive protein (CRP), interleukin 6 (IL-6), and intercellular adhesion molecule 1 (ICAM-1) [5-8].

Recently, more attention has been attracted on vascular endothelial growth factor (VEGF) which is a potent endothelial cell-specific mitogen that promotes angiogenesis and vasodilatation in both physiologic and pathologic processes [9-11]. VEGF is the only growth factor proven to be specific and critical as a mitogen for vascular endothelial cells derived from arteries, veins, and lymphatics, but it is devoid of consistent and appreciable mitogenic activity for other cell types [12].

Pro-atherosclerotic role of VEGF, with a direct relationship with the incidence of coronary artery disease was also revealed [13]. VEGF concentration is in a strong connection with oxidative stress markers, and native and oxidized low density lipoproteins as well [14-17]. Additionally, the enlargement of atherosclerotic plaque size is found to be accompanied by increased plaque vascularity, underscoring the intimate relationship between expression of VEGF and neointimal lesion formation within the plaque [15, 16, 18].

Moreover, these abovementioned cytokines appear to be valuable predictors of future cardiovascular events in recent studies [19-21].

Aim

Therefore, the present study aimed to assess the concentrations of VEGF, CRP and IL-6 in patients with confirmed coronary artery disease qualified to coronary artery bypass grafting (CABG), compared to healthy controls. We also investigated the hypothesis whether serum concentrations of examined inflammatory markers are associated with lipids' concentrations in both groups.

Material and Methods

Subjects

In a case-control study, we investigated 38 patients (aged 65.6 ±10.0) with coronary artery disease and qualified to CABG (the study group), and 37 healthy controls (aged 24.3 ±7.6). The study group was composed of consecutive patients who were hospitalized at the cardiac surgery centre from coronary artery disease at any clinical stage (stable or unstable), which was confirmed in a coronary arteriography to be qualified to surgical treatment (at least 50% of artery stenosis). Hypercholesterolemia was diagnosed if total cholesterol exceeded 200 mg/dl, regardless pharmacological treatment. The control group consisted of healthy volunteers with proper lipids' concentrations, and negative history of pharmacological treatment or any hospitalization from heart condition. Informed written consent was obtained from all participants and the study was approved by the local ethics committee.

Health condition assessment

All subjects were invited to fulfil the questionnaire regarding the history of previous and current diagnosed diseases and any pharmacological treatment. A standardized D-mode echocardiography was performed in all hospitalized patients. The characteristics of subjects are shown in Table I. In the study group, 28 subjects were diagnosed with hypertension and 7 with diabetes mellitus. The study group people were older and more frequent in male gender. There were no subjects with diabetes, hypertension, low ejection fraction, renal failure and any neurological impairment in the control group. Statistically significant between-group differences were also noticed in relation to the CCS and NYHA classes, and pharmacological treatment with statins.

Laboratory tests

Total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride concentrations were analyzed by using standardized methods with commercially available kits. Serum concentrations of CRP were analyzed by particle-enhanced immunonephlometry using the N High Sensitivity CRP Reagent (Dade Behring INC., Marburg, Germany) with the assay sensitivity limit of 0.175 mg/l and a coefficient of variation of ~5%. Serum concentrations of IL-6 were assessed

Tab. I. Subjects' characteristics

Variable		Study group (n = 38)	Control group (n = 37)	Total (n = 75)	p
Gender (F/M) (n/n)		14/24	35/2	49/26	< 0.0001
Age (years)		65.6 ±10.0	24.3 ±7.6	45.2 ±22.6	< 0.0001
BMI (kg/m^2)		26.9 ±4.5	24.2 ±5.6	25.2 ±5.2	0.07
HT (n)		28	0	28	< 0.0001
DM (n)		7	0	7	< 0.0001
CCS class (n)	I	14	39	53	< 0.0001
	II	10	0	10	
	III	15	0	15	
	IV	0	0	0	
NYHA class (n)	I	27	39	66	0.0008
	II	8	0	8	
	III	4	0	4	
	IV	0	0	0	
EF < 40% (n)		2	0	2	0.2
Renal failure (n)		1	0	1	0.3
Neurological impairment (n)		0	0	0	–
Statins (n)		28	0	28	< 0.0001

F – female, M – male, HT – hypertension, DM – diabetes mellitus, CCS – Canadian Cardiac Society, NYHA – New York Heart Association, EF – ejection fraction.

using the ELISA for Quantitative Detection of Soluble Human IL-6 (Beder MedSystems GmbH, Vienna, Austria) with the assay sensitivity limit of 0.92 pg/ml and a coefficient of variation of ~3.4%. Serum concentrations of VEGF were analyzed with the use of the Human VEGF ELISA Kit (RayBio INC., Norcross GA, USA) with the assay sensitivity limit of 4.0 pg/ml and a coefficient of variation less than 10%.

Statistical analysis

Statistical analysis was performed with the use of Statistica 7.1 (Statsoft Poland) procedures. Quantitative variables are presented as means and standard deviations. Qualitative data are presented as crude values. For continuous data, between-group differences were assessed with the use of Student's *t*-test (for normally distributed variables) or Mann-Whitney's *U*-test (for not normally distributed variables). For categorical data, chi-square test or Fisher's exact test were used to estimate between-group differences. Normality of continuous data distribution was assessed with Shapiro-Wilk's W-test. Correlation between data (especially in relation to lipid profile and cytokines' concentrations) was assessed with the use of Spearman's coefficient of correlation. The accurate impact of lipid concentrations on investigated cytokines' levels was re-assessed in multivariate analysis to take into account the possible noise of confounders. The statistical adjustment for age, gender and subjects' clinical profile was performed in the model of linear regression, in which dependent variables were cytokines' concentrations and independent variables were consecutive lipid fractions. All tests were two-tailed. $P < 0.05$ was considered statistically significant.

Results

Table II shows the fasting concentrations of total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides measured in investigated subjects. In the study group, all investigated lipid concentrations were statistically significantly higher in comparison with healthy subjects.

In relation to cytokines' concentrations, it was revealed that subjects in the study group had statistically significantly higher CRP and VEGF concentrations compared to the control group (Tab. III). There was no important difference between groups regarding IL-6 concentration.

Table IV shows Spearman's coefficients of correlation between lipids' concentrations and cytokines' concentrations. In all subjects, VEGF was positively correlated with total cholesterol level ($R = 0.42$; $p = 0.03$) and LDL concentration ($R = 0.48$; $p = 0.01$), and CRP was negatively correlated with HDL level ($R = –0.45$; $p = 0.02$). In the control group CRP was also negatively correlated with HDL concentration ($R = –0.88$; $p = 0.002$). No statistically significant correlations were found in the study group.

Tab. II. Lipids' profile

Variable	Study group	Control group	Total	p
TCh	187.3 ±39.6	154.4 ±27.4	171.1 ±37.8	< 0.0001
HDL	61.8 ±56.3	65.4 ±19.7	63.5 ±42.2	< 0.0001
LDL	109.9 ±35.0	77.8 ±25.7	93.6 ±34.4	< 0.0001
TG	171.6 ±110.7	72.5 ±33.8	122.7 ±95.7	< 0.0001

TCh – total cholesterol, HDL – high density lipoproteins, LDL – low density lipoproteins, TG – triglycerides.

Tab. III. Cytokines' concentrations

Variable	Study group	Control group	Total	p
IL-6	8.0 ±5.8	6.3 ±2.9	7.2 ±4.7	0.3
CRP	13.7 ±40.5	1.0 ±0.9	9.0 ±32.5	0.005
VEGF	8246.6 ±7730.1	3968.6 ±4158.7	5985.4 ±6431.3	0.008

IL-6 – interleukin 6, CRP – C-reactive protein, VEGF – vascular endothelial growth factor.

Tab. IV. Correlation between lipids' concentrations and cytokines' concentrations

	IL-6			CRP			VEGF		
	Total	Study group	Control group	Total	Study group	Control group	Total	Study group	Control group
TCh	–0.03 (0.9)	0.13 (0.6)	0.20 (0.6)	0.12 (0.6)	–0.13 (0.6)	–0.09 (0.8)	0.42 (0.03)	0.34 (0.2)	0.26 (0.5)
HDL	0.09 (0.7)	–0.24 (0.4)	0.02 (0.9)	–0.45 (0.02)	–0.33 (0.2)	–0.88 (0.002)	–0.22 (0.3)	0.19 (0.5)	–0.36 (0.3)
LDL	0.05 (0.8)	0.20 (0.4)	0.39 (0.3)	0.23 (0.3)	0.01 (0.9)	0.20 (0.6)	0.48 (0.01)	0.39 (0.1)	0.39 (0.3)
TG	–0.18 (0.4)	–0.03 (0.9)	–0.01 (0.9)	0.18 (0.4)	–0.12 (0.6)	0.20 (0.6)	0.07 (0.7)	–0.29 (0.3)	0.21 (0.6)

Values are Spearman's rank correlation coefficients and 'p' values (in parentheses), TCh – total cholesterol, HDL – high density lipoproteins, LDL – low density lipoproteins, TG – triglycerides, IL-6 – interleukin 6, CRP – C-reactive protein, VEGF – vascular endothelial growth factor.

The results of multivariate analysis are presented in Table V. After adjustment for gender, age, pharmacological treatment with statins and clinical profile, CRP was dependent on total cholesterol (b = 0.64; p = 0.004), HDL (b = –1.25; p < 0.0001) and triglyceride (b = –0.25; p = 0.02) concentrations, and VEGF was dependent on LDL level (b = 41.7; p = 0.05).

Discussion

The presented study aimed to assess the concentrations of inflammatory markers, VEGF, CRP and IL-6 in patients with coronary artery disease with confirmed hypercholesterolemia, compared to healthy controls, and to correlate examined inflammatory markers with lipids' concentrations.

Many researches have examined the potential role of inflammatory biochemical markers as predictors of cardiovascular risk in order to complement traditional risk factors, or to identify new categories of individuals prone to the development or even complications of atherosclerosis. Among these molecules, interleukin IL-6, an acute inflammatory cytokine produced by activated macrophages, endothelial cells and vascular smooth muscle cells could act as a pro-inflammatory and procoagulant agent, with potential major implications on atherosclerosis progression and thrombotic complications [5, 6]. It has been shown that IL-6 stimulates macrophages to secrete monocyte chemoattractant protein 1, promotes the expression of adhesion molecules and the secretion of other cytokines by endothelial cells, and the proliferation and the migration of smooth muscle cells [22].

However in the current study we found no difference in IL-6 concentrations between patients with confirmed atherosclerosis and healthy subjects and no relationships between lipids' concentrations and IL-6 level. We therefore revealed that subjects in the study group had statistically

Tab. V. Impact of lipids' concentrations on cytokines' concentrations, after adjustment for possible confounders, in multivariate analysis

Dependent variable	Independent variable	'b'*	'b' Std.	t(66)	R^2	p
IL-6	TCh	–0.03	0.02	–1.64	0.06	0.1
	HDL	0.02	0.01	1.33	0.05	0.2
	LDL	–0.01	0.02	–0.73	0.04	0.5
	TG	–0.01	0.01	–1.65	0.06	0.1
CRP	TCh	0.64	0.20	–3.17	0.47	0.004
	HDL	–1.25	0.14	8.54	0.82	< 0.0001
	LDL	–0.45	0.24	–1.86	0.33	0.08
	TG	–0.25	0.1	–2.48	0.39	0.02
VEGF	TCh	7.62	23.2	0.32	0.17	0.7
	HDL	–10.34	21.7	–0.47	0.17	0.6
	LDL	41.72	21.7	1.92	0.23	0.05
	TG	5.85	9.96	0.59	0.17	0.6

*IL-6 – interleukin 6; CRP – C-reactive protein; VEGF – vascular endothelial growth factor; TCh – total cholesterol; HDL – high density lipoprotein; LDL – low density lipoprotein; TG – triglycerides; 'b' – coefficient of linear regression; 'b' Std. – standard error; t(66) – the value of t-test; R^2 – coefficient of determination; p – p-value for t-test; * adjustment for gender, age, study/reference group, treatment with statins and subjects' clinical profile (see Tab. I).*

significantly higher CRP levels compared to the control group and CRP was negatively correlated with HDL level, also the control group. Besides, in multivariate analysis CRP was positively correlated with total cholesterol and negatively with HDL and triglycerides concentrations. On the one hand, IL-6 is a major determinant of CRP hepatic synthesis [22] and may be a better predictor of cardiovascular events than CRP concentrations in older subjects [23]. Consequently, these observations should support our findings in relation to CRP and lipids. But on the other hand, IL-6 levels are associated with stable atherosclerotic lesions independently of traditional risk factors [5, 6] and these data are in agreement with our findings. Moreover, plasma IL-6 concentrations are found to have a noticeable circadian variation [24] that may result in misinterpretation of the results. Reinforcing the view that cardiovascular disease involves an ongoing inflammatory response, prospective epidemiologic studies in asymptomatic individuals revealed that plasma CRP may have predictive value in cardiovascular disease risk assessment [7, 25, 26] with a direct effect on the progression of atherosclerosis [5, 27].

VEGF seems to be an interesting marker of atherosclerosis as well as IL 6 and CRP. Not only VEGF should be considered as a factor involved in new vessels formation, but also in the atherosclerotic plaque development, being directly correlated with lipids' profile disturbances. We found that participants with coronary heart disease had statistically significantly higher VEGF concentration in comparison to healthy controls. Additionally, VEGF was strongly dependent on LDL level (b = +41.7; p = 0.05).

One of the potential mechanisms leading to increased secretion of VEGF by endothelial cell might be endothelial dysfunction. Decreased production of NO at the early stage of atherosclerosis is leading to reduction in oxygen supply to the artery wall. Subsequently, the local ischemia is followed by activation of hypoxia-inducible factor, a transcription factor that regulates the expression of proangiogenic factors such as VEGF [28].

We investigated serum level of this mitogen following the results of Kmura et al. who showed that serum (but not plasma) VEGF level in a population including healthy adults is closely associated with risk factors for atherosclerosis [14]. In our research, VEGF and CRP serum concentrations were significantly higher in hypercholesterolemic than in normocholesterolemic subjects. Oxidative LDL-cholesterol is stated to induce VEGF production in different cells including smooth muscle cells, macrophages, or endothelial cells [29, 30], which may explain the increased VEGF serum levels in our study group in comparison with subjects with proper lipids' concentrations.

The results of clinical and epidemiological data demonstrate that the HMG-CoA-reductase-inhibitors (statins) have direct anti-inflammatory effect beside the cholesterol-lowering activity. These additional effects of statins might explain partly the clinical benefits of these drugs and these effects may also have impact on our results. Statins down-regulate the expression of several inflammatory markers released by endothelial cells, which in turns attenuates the progress of inflammatory diseases [13, 31]. The ability of statins to inhibit the activation of transcription factors NF-κB, might be relevant for the decrease of serum levels of IL-6 and CRP, and may explain the lack of difference in concentrations between examined subjects in our study [15, 30, 31].

It should be also underlined that in relation to biological impact of VEGF on the development of atherosclerosis, the results obtained in humans are different from those on animal models [11, 16]. The issue gives a serious concern and raises multiple questions. The vast majority of evidence supports the role of VEGF in atherosclerosis progression [14, 15, 32]. However, some contradictory data has been published [13, 33].

There are possible limitations of concluding in the presented study. First of all, the small sample size results in the lack of generalizability of our data at the population level. However, clinical experimental trials usually include such a number of participants with no major difficulties in concluding in relation to the particular group of examined patients. Also, having only a single assessment of investigated makers and lipids' concentrations weaken the strength of evidence, this is more prone to be affected by measurement error or within-subjects variability then. Finally, although the design used in the present study was successfully implemented by the others [34], the marked discrepancy in demographic and clinical profile of subjects in the study and control groups may result in imprecise conclusions drawn on the basis of given results. It may explain the differences seen between univariate and multivariate analyses. We believe that the adjustment for possible confounders in the latter gives more reliable results from the methodological point of view, however we did not take into consideration additionally approved determinants of VEGF, CRP and IL-6, i.e. smoking habit, body composition, and morphological and biochemical parameters of the blood [7, 14, 27, 35].

Conclusions

In conclusion, patients with coronary artery disease had higher CRP and VEGF concentrations compared to healthy subjects but there was no difference in relation to the IL-6 concentration. In univariate analysis, VEGF was positively correlated with total cholesterol and LDL concentrations, and CRP was negatively correlated with HDL level. After adjustment for clinical and demographic data, CRP was statistically significantly compared with total cholesterol but negatively associated with HDL and triglyceride concentrations, and VEGF was strongly positively correlated with LDL level.

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