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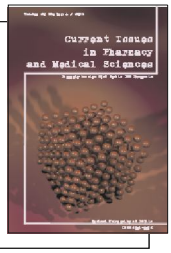

Lipoprotein-associated phospholipase A2 (Lp-PLA2) and high sensitivity C-reactive protein (hsCRP) levels, and extends coronary artery disease (CAD) patient after one year observation

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ABSTRACT

A serum lipid profiles high sensitivity C-reactive protein (hsCRP) levels are established risk factors for atherosclerosis, and a powerful predictor of future myocardial infarction or cardiac death among apparently healthy individuals. Lipoprotein-associated phospholipase A2 (Lp-PLA2) is know but not as cardiovascular risk factor. The aim of this study was to investigate serum Lp-PLA2 activity and arterial stiffness and others atherosclerosis biochemistry markers in patients with stable coronary artery disease. We studied 17 consecutive patients (women, n=6 and men, n=11), mean age was 61 years, with stable coronary artery disease (CAD), hospitalized in the Department of Cardiology Cardinal Wyszyński Hospital in Lublin in 2012 and 2013. The patients with acute and chronic kidney disease, liver diseases, active autoimmune disease, malignancy, thyroids diseases or alcohol disease were excluded from the analysis. The patients had worse laboratory parameters than the reference group. We showed significant positive correlation between serum level LpPLA2 and extends coronary disease in patients who had upper LpPLA2 levels in year observation. We concluded that dyslipidemia together with hsCRP and Lp-PLA2 and monitoring of its levels may be good markers to predict ACS or other CAD events and vessels lesions in asymptomatic patients with CAD. However, these results require further studies.

Keywords: lipoprotein-associated phospholipase A2, high sensitivity C-reactive protein, coronary artery disease

INTRODUCTION

In European countries, it can be estimated that 20 000–40 000 per million people suffer from CAD [7]. In Poland, million people suffer from CAD [2]. Stabile angina pectoris is common type of coronary artery disease. CAD leads to high risk of myocardial infarction, heart failure and disabling disorder [2, 9, 11]. Therefore, novel diagnostic methods and new treatment strategy is very important.

C-reactive protein (CRP) is a non-specific indicator of the acute inflammatory state. It is used for detecting the inflammatory process. It is acute-phase protein primarily synthesized in the liver and fat cells (adipocytes), its release is stimulated by interleukin 6 (IL-6) which is produced predominantly by macrophages. CRP plays a key role in complement binding to foreign and damaged cells and enhances phagocytosis by macrophages in the innate immune response [4, 5].

Normal concentration in healthy human serum is usually lower than 10 mg/l. A high-sensitivity CRP (hs-CRP) test measures low levels of CRP with sensitivity down to 0.04 mg/l. A role for inflammation in atherosclerosis is known and much more attention has been paid to the role of inflammation in atherosclerosis. Inflammation within the vessels wall connected with invasion white blood cell plays a key role in destabilization and rupture of atherosclerotic plaques, leading to acute cardiovascular (CV) events. High sensitivity C-reactive protein (hsCRP) level is associated with increased cardiovascular disease (CVD) risk [3, 9, 17, 18].

Catalyzed hydrolysis of phospholipids takes place with the participation of phospholipases. Phospholipases are a diverse group of enzymes, which have different functions in the human body. They are specific enzymes of intracellular organ . The common feature of phospholipases are hydrolysis of ester bonds. Phospholipases are

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divided into four major groups, e.g., A1, A2, C and D. Phospholipases hydrolyzing binding of phospholipids in the position syn-1 or syn-2 are called respectively A-1 and A-2 [14].

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a calcium independent enzyme. It is produced by monocytes, macrophages, limfocytes T and mastocytes in vessel wall [6, 15]. In human plasma, Lp-PLA2 is bound to apolipoprotein containing aproteins B (apo B), e.g., LDL (80-85%), VLDL, IDL and to some extent also to high-density lipoprotein (HDL) (15–20%). Lp-PLA2 has an ability to hydrolyze oxidized phospholipids and release lysophosphatidylocholone and oxidized non-estrified fatty acid, both of which are pro- inflammatory, and ultimately lead to foam cell formation. It progresses atherosclerosis, destabilization of atherosclerosis plates and promotes ACS events [15].

The aim of this study was to investigate serum lipids, hsCRP and LpPLA2 level, and to analyze correlation between lipoprotein-associated phospholipase A2 (Lp-PLA2), and high sensitivity C-reactive protein (hsCRP) level and extends coronary artery disease (CAD) patient after one year observation.

MATERIAL AND METHODS

We studied 17 (women, n=6 and men, n=11) patients with stable coronary artery disease (CAD). Patients were hospitalized in the Department of Cardiology Cardinal Wyszyński Hospital in Lublin, in April-May 2012 and they carried on control ambulatory visit after one year. 61

Thirteen 39±14.7, coronary artery diseaseVenous blood was drawn after a 14-hour overnight fasting, and plasma was obtained by centrifugation at 3000 rpm at 4^{o}C immediately after blood collection. The total cholesterol (TC), LDL-C, HDL-C was estimated by the enzymatic-colorimetric method (Roche tests). Triglycerides (TG) were determined using the standard enzymatic technique by Roche tests. Concentration of hsCRP was measured with immunonephelometric methods, Simens Healthcare Diagnostic Product GmbH on a Dade Behring nephelometer BNII System, Germany.

Coronary lesion vessels are described by SYNTAX score and number of lesion vessels. SYNTAX score is an angiographic tool used in grading the complexity of CAD. Each coronary lesion with a Diameter Stenosis ≥50% in vessels ≥1.5 mm must be scored. We used the calculation of the SYNTAX score (www.syntaxscore.com).

Statistical analysis was performed using the t-Student test. The relation between parameters was examined by Spearman's correlation analysis. The statistical significance of all variables was established at $p<0.05$. Statistical analysis was performed using the STATISTICA program (StatSoft, Krakow, Poland).

RESULTS

Patients with acute coronary syndromes (ACS) in history where 59% (n=10) of studied population (unstable angina n=0; no ST elevation myocardial infarction n=2, ST elevation myocardial infarction n=8). Studied population without ACS 41% (n=7). Studied group consisted of patients with arterial hypertension 88% (n=15), diabetes mellitus 71% (n=12), obesity 47% (n=8), overweight 41% (n=7), and 52% (n=9) patients smoked in. Acetylsalicylic acid (75–150 mg/D) was received by patients 94% (n =16), all patients were treated with statins. The patients with acute and chronic kidney disease.

Clinical and laboratory parameters of patients with CAD are presented in Table 1.

Table 1. Clinical and laboratory parameters patients with CAD before and after one year

	N	Mean	SD	Mean after one year	SD	P<
Pcell Age (years)	17	60.8824	4.80732	–	–	–
BMI (kg/m^2)	17	30.3708	4.01582	–	–	–
hsCRP(mg/l)	17	35.9045	49.55628	–	–	–
LpPLA2	17	103.8047	37.11259	92.8559	22.96749	NS
TCh (mg/dl)	17	163.7465	45.77505	151.3125	27.31964	NS
LDL (mg/dl)	17	90.7935	42.06739	83.4250	23.41394	NS
HDL (mg/dl)	17	45.6059	10.71157	43.9375	10.30514	NS
TG (mg/dl)	17	153.1653	73.34685	120.1563	44.18737	0.05

The patients had worse laboratory parameters than the reference group. The patients with CAD after one year treatment had a significant decreased concentration of TG level ($p= 0.05$), but not of TC, HDL, LDL levels. The correlation between LpPLA2 and other variables in all studied patients has not been shown. Moreover, the analysis of LpPLA2 levels did not show any significant association between diabetes mellitus and ACS in history. LpPLA2 levels were not connected with extends of coronary disease in all studied patients.

Next, we divided patients on two subgroups: with growing LpPLA2 levels (n=8; $p<0.011$) and lowering LpPLA2 levels (n=9; $p<0.011$) after one year observation. Extends coronary disease in growing LpPLA2 subgroup was 3-vessels disease three patients, 2-vessels disease two patients, 1-vessels disease two patients, without lesion vessels one patient. Than, we showed a significant positive correlation between serum level of LpPLA2 and extends coronary disease (SYNTAX score versus LpPLA2 levels) in patients who had growing LpPLA2 levels, and close to significance positive correlation between serum level LpPLA2, and numbers of lesion vessels and numbers of percutaneous coronary interventions (PCI) in history (Table 2).

DISCUSSION

Markers of systemic inflammation, such as C-reactive protein (CRP) associated with increased cardiovascular disease (CVD) risk in the general population are independent for age and gender [2, 7]. Although some ethnic

differences in the hsCRP levels have been reported between other ethnic groups [10].

Table 2. Correlation between LpPLA2 and SYNTAX SCORE. and No. of PCI and No. of lesion vessels in patients with growing LpPLA2 after one year

	R	P<
Pcell LpPLA2[1] v SYNTAX SCORE	0.739	**0.036**
LpPLA2 v No. of PCI[2]	0.692	**0.057**
LpPLA2 v No. of lesion vessels	0.704	**0.051**

[1] LpPLA2 - Lipoprotein-associated phospholipase A2
[2] PCI –Percutaneous coronary interventions

High sensitivity serum C-reactive protein (hsCRP) is associated with cardiovascular disease risk in a variety of clinical settings including healthy people, selected high-risk patients with traditional risk factors and patients diagnosed with cardiovascular diseases [9]. hsCRP level is a powerful predictor of future myocardial infarction and cardiac death among subject without CAD symptoms [3, 12].

Many studies showed that high serum concentration of hsCRP was associated with stenotic coronary vessels [8]. However, these studies were controversial. Taniguchi et al. reported correlations between concentration of hsCRP and the stenotic coronary vessels in patients [17]. Azar et al. reported no correlations between hsCRP level and the extent score in 98 patients with the stenotic vessels [1]. However, Taniguchi et al. showed something else. They did not report correlations between hsCRP levels and extend of coronary stenosis in all study population but after the exclusion of patients who were received statins, the plasma hsCRP levels associated with the presence and extent of coronary artery stenosis in patients with stable CAD [17]. We did not show any correlation between hsCRP versus LpPLA2 and extends of coronary disease because we had to small group and all our patients were treated of statins.

European Guidelines on cardiovascular disease prevention in clinical practice version 2012 have shown that high-sensitive CRP may be used in persons at moderate CVD risk. However, it should not be measured in asymptomatic low-risk individuals, and high-risk patients to assess 10 year risk of CVD, because several weak points exist, e.g., multiplicity of confounders or lack of precision.

Lipoprotein-associated phospholipase A2 may be measured as part of a refined risk assessment in patients at high risk of a recurrent acute atherothrombotic events but it is 'second-line' marker for CVD risk estimation [11].

Lipoprotein-associated phospholipase A2 (Lp-PLA2) represents a potential cardiovascular risk marker, given its correlations with coronary disease, stroke and vascular death. Sabatine et al. have shown that higher baseline Lp-PLA2 levels were significantly associated with male sex, Caucasian race, current tobacco use, prior MI, lack of prior coronary revascularization, higher serum cholesterol level, and lack of lipid-lowering therapy. Authors have also shown significant stepwise increase in the cumulative incidence of the composite of cardiovascular death, MI, coronary revascularization, hospitalization for UA, or stroke [13]. In our study, we did not show any associations.

Lp-PLA2 mass and activity were associated with risk of incident CVD events also in older adults and there was a significant additive effect when the biomarkers CRP and Lp-PLA2 were combined [16]. All authors described role of Lp-PLA2 as a cardiovascular risk factor. Our study also revealed Lp-PLA2 as a marker in extends of coronary disease.

CONCLUSION

We suggest that dyslipidemia together with hsCRP and Lp-PLA2, and monitoring of their levels may be good markers to predict ACS or other CAD events and vessels lesions in asymptomatic patients with CAD. However, these results require further studies.

REFERENCES

1. Azar RR, Aoun G, Fram DB, Waters DD, Wu AHB, Kiernan FJ.: Relation of C-reactive protein to extent and severity of coronary narrowing in patients with stable angina pectoris or abnormal exercise tests. *Am. J. Cardiol.*, 86, 205, 2000.
2. Banasiak W., Gierelak G., Ponikowski P.: *Stabilna choroba wieńcowa. Trudne pytania i wątpliwości kliniczne.* Wydawn. MP., ISBN 978, 83-7430-163-3, 2008.
3. Bogavac-Stanojević N., Jelić-Ivanović Z., Spasojević-Kalimanovska V., Spasić S., Kalimanovska-Oštrić D.: Lipid and inflammatory markers for the prediction of coronary artery disease: A multi-marker approach. *Clin. Biochem.*, 40, 1000, 2007.
4. Danesh J., Pepys M.B.: C-Reactive protein and coronary disease: is there a causal link? *Circulation*, 120, 2036, 2009.
5. Danesh J., Wheeler J.G., Hirschfield G.M., et al.: C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N. Engl. J. Med.*, 350, 1387, 2004.
6. Dullaart R., Constantinides A., Perton F.G.: Plasma cholesteryl ester transfer, but not cholesterol estrification, is related to lipoprotein-associated phospholipase A2: possible contribution to an atherogenic lipoprotein profile. *J. Clin. Endocrinol. Metab.*, 96(4),1077, 2011.
7. Fox K., Alonso Garcia MA., Ardissino D.: Guidelines on the management of stable angina pectoris. *Eur. Heart J.* 7(8), 535, 2006.
8. Khera A., de Lemos J.A., Peshock R.M., et al.: Relationship between C-reactive protein and subclinical atherosclerosis. *The Dallas Heart Study. Circulation,* 113, 38, 2006.
9. Madjid M. and Willerson J.T.: Inflammatory markers in coronary heart disease. *Brit. Med. Bull.*, 100, 23, 2011.
10. Pai J.K., Pischon T., Ma J., et al.: Inflammatory markers and the risk of coronary heart disease in men and women. *N. Engl. J. Med.*, 351, 2599, 2004.
11. Perk J., Backer G., Gohlke H., et al. : European Guidelines on cardiovascular disease prevention in clinical practice version 2012. *Eur. Heart J.*, 33, 1635, 2012.
12. Ridker P.M., Morrow D.A.: C-reactive protein, inflammation, and coronary risk. *Cardiol. Clin.*, 21(3), 315, 2003.

13. Sabatine M.S., Morrow D.A., O'Donoghue M. et al.: Prognostic utility of lipoprotein-associated phospholipase A2 for cardiovascular outcomes in patients with stable coronary artery disease. Arterioscler. *Thromb. Vasc. Biol*., 27, 2463, 2007.
14. Sadurska B, Szumiło M.: Fosfolipazy A w komórkach ssaków – budowa, właściwości, rola fizjologiczna i patologiczna. *Post. Hig. Med. Dośw*., 59, 116, 2005.
15. Silva I.T., Mello A.P., Ma J.: Antioxidant and inflammatory aspects of lipoprotein-associated phospholipase A2 (Lp-PLA2): a review. *Lipid. Health. Dis*., 10, 170, 2011.
16. Swords J.N., Solomon C., Cushman C., et al.: Lipoprotein-associated phospholipase A2 (Lp-PLA2) and risk of cardiovascular disease in older adults: results from the cardiovascular health study. *Atherosclerosis*, 209(2), 528, 2010.
17. Taniguchi H. Momiyama Y., Ohmori R., et al.: Associations of plasma C-reactive protein levels with the presence and extent of coronary stenosis in patients with stable coronary artery disease. *Atherosclerosis,* 178, 173, 2005.
18. Zebrack JS, Muhlestein JB, Home BD, Anderson JL.: The Intermountain Heart Collaboration Study Group. C-reactive protein and angiographic coronary artery disease: independent and additive predictors of risk in subjects with angina. *J. Am. Coll. Cardiol*., 39,632, 2002.