Kardiologia Polska 2016; 74, 6: 570–575; DOI: 10.5603/KP.a2015.0238 ISSN 0022–9032

ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Is plasma-soluble CD36 associated with density of atheromatous plaque and ankle–brachial index in early-onset coronary artery disease patients?

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Abstract

Background: CD36 is a major macrophage scavenger receptor for oxidised low-density lipoprotein particles. Soluble CD36 (sCD36) is circulating as a ligand-bound complex and may be present in microparticles shed from cells such as platelets, monocytes/macrophages, or adipocytes. Positive association of plasma sCD36 with insulin resistance has been reported, and it has been proposed that sCD36 might represent a marker of macrophage activation and inflammation leading to atherosclerosis. Recently we have identified an association between *CD36* polymorphism and low thickness of atheromatous plaque, suggesting its protective effect against atherosclerosis development.

Aim: To obtain insight into the relationship between plasma concentration of sCD36 and radiological parameters of atherosclerosis in patients with early-onset coronary artery disease (CAD).

Methods: The study group comprised 70 clinically stable patients (18 women and 52 men) with early CAD (aged no more than 50 years for men and 55 years for women). Fasting blood sample was taken for serum glucose, lipid profile, ApoA1, ApoB, Lp(a), and plasma sCD36 protein measurements. Each subject's weight, height, waist and hip circumference, and systolic and diastolic blood pressure were measured, and the body mass index, waist-to-hip ratio, and mean arterial pressure were calculated. Doppler ultrasound examinations of carotid and peripheral arteries were performed in all patients. Thickness of intima–media complex (IMC) of common carotid (CCA) and brachial arteries, as well as density and thickness of atheromatous plaque at CCA bifurcation, were measured with M'Ath programme. Plasma concentrations of CD36 antigen were measured by ELISA. Correlations between quantitative variables and sCD36 plasma concentration were assessed with the Spearman rank correlation coefficient (Rs). Associations between qualitative variables and sCD36 plasma concentration were tested with the Mann-Whitney U test.

Results: We observed no significant correlations between sCD36 concentration and radiological parameters of atherosclerosis. We found only borderline significant negative correlation of sCD36 concentration with thickness of IMC of left brachial artery. We also observed a significantly negative correlation with CCA plaque density, but only in the female subgroup and on the right side. Borderline higher sCD36 plasma concentrations were observed in patients with lower ankle–brachial index value (< 0.9).

Conclusions: The results of the study show no strong associations and do not prove either detrimental or beneficial influence of sCD36 on radiological parameters of atherosclerosis. Further research is necessary to assess the association of high plasma sCD36 concentrations with the risk of plaque instability in patients with early-onset CAD.

Key words: plasma CD36, coronary artery disease, plaque density, ankle–brachial index

Kardiol Pol 2016; 74, 6: 570–575

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Received: 08.04.2015 **Accepted:** 22.10.2015 **Available as AoP:** 27.11.2015

INTRODUCTION

CD36 is a major macrophage scavenger receptor for oxidised low-density lipoprotein (LDL) particles [1] and is believed to play a critical role in the initiation and progression of atherosclerosis through its ability to bind and internalise modified LDL, facilitating formation of lipid-engorged macrophage foam cells [2–4]. In addition, the 7q chromosome region, containing the *CD36* gene, has been linked to components of metabolic syndrome in several genome-wide association studies [5, 6]. It has been shown [7, 8] that soluble CD36 (sCD36) is circulating as ligand-bound complex and may be present as an unbound protein or a peptide fraction thereof, or may be present in microparticles shed from cells such as platelets, monocytes/macrophages, or adipocytes after being triggered by various stimuli. Tontonoz et al. [9] hypothesised that decreased sCD36 level is a result of lower activity of endogenous peroxisome proliferator-activated receptor gamma (PPARγ). Plasma CD36 is released into circulation during cell apoptosis, such as that taking place after cholesterol accumulation in foam cells [10, 11]. Positive association of plasma sCD36 concentration with insulin resistance has been reported, and it has been proposed that sCD36 might represent a marker of macrophage activation and inflammation leading to atherosclerosis [12, 13].

We have recently identified an association between *CD36* polymorphism and low thickness of atheromatous plaque, suggesting its protective effect against atherosclerosis development [14]. The aim of this study was to obtain insight into the relationship between plasma concentration of sCD36 and radiological parameters of atherosclerosis in patients with early-onset coronary artery disease (CAD).

METHODS

The study group comprised 70 clinically stable patients (18 women and 52 men) with early-onset CAD (men less than 50 years old and women less than 55 years old; age of all patients 49 ± 6 years). All patients were Polish residents hospitalised in the Department of Cardiology of the County Hospital in Szczecin (north-western Poland) and then referred to the outpatient clinic in the years 2008–2011. The study complies with the principles outlined in the Declaration of Helsinki and was approved by our institutional Ethics Committee. Informed consent was obtained from each patient. The criteria for early-onset CAD diagnosis and characteristics of the study group were presented in our previous study [14]. Fasting blood sample was taken for serum glucose, lipid profile (total, high-density lipoprotein [HDL] and LDL cholesterol, and triglycerides), ApoA1, ApoB, Lp(a), and plasma sCD36 protein measurements. In addition, the weight, height, waist and hip circumference, and systolic and diastolic blood pressure of each patient were measured, and the body mass index, waist-to-hip ratio, and mean arterial pressure calculated. Doppler ultrasound examinations of carotid and peripheral arteries were performed in all patients. Thickness of the intima–media complex (IMC) of the common carotid artery (CCA) and brachial artery, and the density and thickness of atheromatous plaque at CCA bifurcation were measured with M'Ath programme [15]. Density measurement was based on the intensity of reflection from the plaque dependent on calcium deposits. The ankle–brachial index (ABI) was calculated by dividing the systolic blood pressure (SBP) in the arteries at the left and right ankle (posterior tibial artery) or foot (anterior tibial artery) by the higher of the two SBPs in the arms.

Plasma concentrations of human CD36 antigen (Platelet Membrane Glycoprotein IV) were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (EIAab, Wuhan EIAab Science Co., Ltd., China) according to the manufacturer's protocol, as previously published by Krzystolik et al. [16].

Correlations between quantitative variables and sCD36 plasma concentration were assessed with the Spearman rank correlation coefficient (Rs). Associations between qualitative variables and sCD36 plasma concentration were tested with the Mann-Whitney U test. P-values < 0.05 were considered statistically significant.

RESULTS

The clinical data of the study group are presented in Table 1. Significantly higher soluble CD36 plasma concentrations were found in females. Therefore, all CAD patients were divided into subgroups of men and women for further analysis. Correlations between quantitative variables and

Table 1. Characteristics of the study group (n = 70)

Parameter	Value
Glucose [mg/dL]	105 ± 23.5
Total cholesterol [mg/dL]	167 ± 34.3
HDL-cholesterol [mg/dL]	48.1 ± 12.0
LDL-cholesterol [mg/dL]	96.9 ± 29.8
Triglycerides [mg/dL]	139 ± 58.9
Lp(a) [mg/dL]	44.0 ± 53.8
ApoB/ApoA1	0.51 ± 0.13
Systolic BP [mm Hg]	128 ± 15.0
Diastolic BP [mm Hg]	77.6 ± 8.6
MAP [mm Hg]	94.3 ± 9.3
Waist-to-hip ratio	0.97 ± 0.10
Body mass index [kg/m^2]	28.4 ± 4.2
History of hypertension	66%
Diabetes (type 2)	13%
Past MI	66%
Age of the first MI [years]	44.0 ± 6.0

Data are given as mean ± standard deviation; LDL — low-density lipoprotein; HDL — high-density lipoprotein; BP — blood pressure; MAP — mean arterial pressure; MI — myocardial infarction

Table 2. Correlations between circulating soluble CD36 concentration and quantitative parameters of early-onset coronary artery disease (CAD) patients in the whole study group and in the subgroups of CAD males and females

Parameter	Correlations for all CAD patients (n = 70)		Correlations for CAD males (n = 52)		Correlations for CAD females (n=18)	
	Rs	P	Rs	P	Rs	P
ABI right	–0.16	0.18	–0.059	0.67	0.044	0.86
ABI left	–0.14	0.22	–0.061	0.66	–0.068	0.78
ABI mean	–0.16	0.17	–0.074	0.60	–0.090	0.71
IMC cca right	–0.20	0.083	–0.21	0.13	–0.077	0.75
IMC cca left	–0.079	0.50	–0.035	0.80	0.11	0.64
IMC cca mean	–0.18	0.11	–0.099	0.47	–0.079	0.74
IMC ba right	–0.031	0.79	0.018	0.90	0.12	0.61
IMC ba left	–0.22	**0.058**	–0.065	0.65	–0.14	0.55
IMC ba mean	–0.087	0.47	0.044	0.76	–0.11	0.66
PLA thickness left	0.031	0.87	–0.32	0.16	0.22	0.60
PLA length left	0.086	0.66	0.020	0.93	–0.048	0.91
PLA density left	0.019	0.92	–0.10	0.66	0.40	0.33
PLA thickness right	–0.13	0.45	–0.11	0.57	–0.50	0.25
PLA length right	0.0039	0.98	0.11	0.56	–0.56	0.19
PLA density right	0.054	0.75	0.23	0.22	–0.85	**0.016**
PLA thickness mean	0.093	0.57	–0.20	0.31	0.049	0.89
PLA length mean	–0.076	0.63	–0.01	0.95	–0.091	0.80
PLA density mean	–0.069	0.66	–0.027	0.88	-0.097	0.79

ABI — ankle–brachial index; IMC cca — intima–media complex of common carotid arteries; PLA — plaque of common carotid arteries and bifurcation; IMC ba — intima–media complex of brachial arteries; mean — value calculated as mean of measurements of the right and left arteries

CD36 plasma concentration assessed with the Spearman rank correlation coefficient are presented in Table 2. Associations between qualitative variables and CD36 plasma concentration tested with the Mann-Whitney U test are presented in Table 3. There was no association between concentrations of sCD36 and medication or revascularisation treatment, nor with the presence of past myocardial infarction (MI), hypertension, or type 2 diabetes (data not shown).

There were no significant correlations between sCD36 and radiological parameters of atherosclerosis progress in our patients. We observed only weak negative correlation of sCD36 level with IMC of left brachial artery with borderline significance in the whole group. There was also a significant negative correlation with CCA plaque density, but only in the female subgroup and only on the right side. We found borderline higher sCD36 plasma concentrations in patients with lower ABI value (< 0.9).

DISCUSSION

Increased risk of atherosclerosis is associated with lower ABI and higher thickness of IMC [17]. Density of plaque reflects plaque calcification. Lower plaque calcification is associated with plaque instability, but high plaque calcification is associated with predisposition to thrombosis [18, 19]. We studied radiological parameters of atheromatous plaque in an early-onset CAD group. So far, there has been no publication indicating an association between sCD36 and multiple radiological indicators of atherosclerosis in any population. In the current study we found only borderline association of lower ABI value (< 0.9) with higher sCD36 plasma concentrations. We observed significant negative correlation with CCA plaque density, but only in the female subgroup and only on the right side. On the other hand, we observed only weak negative correlation of sCD36 with IMC of the left brachial artery, and it was not significant. The borderline association of higher sCD36 with lower ABI seems to be advantageous, but on the other hand, the association with lower density of plaques may be disadvantageous. Therefore, there is a lack of clear answers on the relationship between plasma concentration of sCD36 and radiological parameters of atherosclerosis in patients with early-onset CAD. Only one previous study demonstrated results similar to ours [20], showing that Caucasian patients with echolucent carotid plaques tended to have higher soluble CD36 levels compared to those with echogenic/heterogenic plaque. However, the association observed in the cited study was not statistically

Table 3. Associations between circulating soluble CD36 concentration and qualitative parameters of early-onset coronary artery disease (CAD) patients in the whole study group and in the subgroups of CAD males and females

Parameter	All CAD patients (n = 70)		CAD males (n = 52)		CAD females (n = 18)	
	sCD36 [mg/L]	P	sCD36 [mg/L]	P	sCD36 [mg/L]	P
ABI ≤ 0.9 (right or left side)	17.54 (6.55)		14.51 (6.06)		24.00 (35.58)	
ABI > 0.9 (right or left side)	12.25 (12.45)	**0.0604**	10.68 (9.98)	0.45	16.82 (15.30)	0.25
IMC cca mean ≥ 0.9 mm	11.68 (10.04)		10.52 (8.36)		17.45 (25.50)	
IMC cca mean < 0.9 mm	12.29 (13.18)	0.33	10.95 (8.77)	0.61	23.32 (16.91)	1.00
PLA present (right or left side)	11.97 (10.02)		10.95 (6.19)		20.81 (18.01)	
PLA absent (right or left side)	15.07 (15.11)	0.72	8.95 (14.19)	0.67	20.05 (11.41)	0.85
PLA length mean ≥ 6.0 mm	11.97 (8.89)		11.48 (5.86)		20.81 (21.65)	
PLA length mean < 6.0 mm	10.73 (10.02)	0.72	9.51 (8.32)	0.42	33.32 (33.17)	0.40
PLA density mean ≥ 70 AU	11.97 (8.67)		10.84 (4.14)		20.81 (25.50)	
PLA density mean < 70 AU	11.89 (11.45)	0.84	11.21 (10.35)	0.96	23.98 (20.60)	0.91
IMC ba mean ≥ 0.6 mm	12.29 (13.28)		10.36 (7.70)		26.93 (26.77)	
IMC ba mean < 0.6 mm	13.29 (12.53)	0.53	11.17 (9.99)	0.93	17.45 (10.65)	0.90

Data are given as median with interquartile range; ABI — ankle–brachial index; IMC cca — intima–media complex of common carotid arteries; PLA — plaque of common carotid arteries and bifurcation; IMC ba — intima–media complex of brachial arteries; mean — value calculated as mean of measurements of the right and left arteries; IMC, plaque length and thickness are expressed in mm

significant (p = 0.087). Moreover, in that publication plasma sCD36 concentration was measured also by enzyme-linked immunoassay, and this evaluation was performed in patients with high-grade internal carotid stenosis (> 70%) treated with carotid angioplasty with stenting.

In our previous study [14] two *CD36* gene polymorphisms were associated with low thickness of atheromatous plaque, suggesting its protective effect against development of atherosclerosis. It is known [21] that CD36 can be detected in atherosclerotic plaques in human aorta and coronary arteries. Its level might be regulated differently with the progress of atherosclerosis in a signalling pathway-coupled cellular uptake of oxidised-LDLs with transcriptional activation of CD36 receptor by PPARγ [9]. In our previous study [16] the higher sCD36 plasma concentrations were significantly positively correlated with HDL-cholesterol and ApoA1 concentrations. We have recently identified [22] an association of *CD36* gene rs3173798 polymorphism with younger age of MI and presence of type 2 diabetes. In the present study there were no differences in sCD36 plasma concentrations between patients with present and absent MI or type 2 diabetes. Moreover, we have shown in another study [16] that there was no association between *CD36* genotypes and sCD36 concentrations.

In fact, our results, which showed no association between concentrations of sCD36 and MI, hypertension, or type 2 diabetes, are not different from the results obtained by other authors. None of the previous studies showed association of sCD36 with diabetes, MI, or hypertension in a direct comparison of groups with and without the disease. Knøsgaard et al. [23] demonstrated a significant association between sCD36 and fasting plasma glucose, but only in a specific population of morbidly obese individuals. Handberg et al. [24] observed positive correlation between sCD36 and fasting plasma glucose only in a subgroup of subjects with high plasma sCD36 concentration, and this correlation lost statistical significance in multivariate analysis. Liani et al. [25] found significantly higher sCD36 levels in patients with type 2 diabetes (aged 64.1 ± 8.7 years) than in healthy subjects (aged 39 ± 12.8 years), but the groups differed in age, while our previous study [16] revealed that older age is a significant independent predictor of higher plasma sCD36.

We also found significantly higher sCD36 plasma concentrations in the female subgroup of CAD patients. Contrary to our results, other authors [24] reported that in clinically healthy Caucasians plasma sCD36 was significantly lower in women than in men, while Chmielewski et al. [26] reported that serum sCD36 concentration is not related to gender in Caucasian chronic kidney disease patients.

It should be noted that the range of plasma sCD36 concentrations measured in our early-onset CAD patients was high. Similarly to our study, high circulating CD36 levels (up to 22.9 μg/mL) measured by ELISA in patients with type 2 diabetes were reported by Alkhatatbeh et al. [27]. Contrary to our results, Lykkeboe et al. [28] reported plasma sCD36 in healthy Caucasian subjects in the range of 0.05–250 ng/mL. In addition, significant differences in plasma sCD36 concentrations measured by two commercial ELISA sCD36 assays were also reported in the same study [28]. In our opinion the analysis of sCD36 is currently hampered by the lack of widely accepted standardised methods. This limitation may constitute a major cause of inconsistent results of different studies concerning sCD36.

CONCLUSIONS

In summary, the present study has some limitations, such as lack of a control group without early-onset CAD and a relatively low number of cases. The lack of strong associations does not resolve doubts about the relationship between sCD36 and radiological parameters of atherosclerosis progress. Further research is necessary to assess the association of high plasma sCD36 concentrations with the risk of plaque instability. These results should be confirmed in a larger group of patients.

Conflict of interest: *none declared*

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Cite this article as: Rać M, Krzystolik A, Rać M et al. Is plasma-soluble CD36 associated with density of atheromatous plaque and ankle–brachial index in early-onset coronary artery disease patients? Kardiol Pol, 2016; 74: 570–575. doi: 10.5603/KP.a2015.0238.

Czy krążący w osoczu CD36 może być markerem gęstości blaszki miażdżycowej i wskaźnika kostka–ramię u pacjentów z chorobą wieńcową rozpoznaną w młodym wieku?

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Streszczenie

Wstęp: CD36 jest receptorem na makrofagach, który odpowiada za internalizację utlenionych cząstek lipoprotein o niskiej gęstości. Rozpuszczalna w osoczu forma CD36 (sCD36) krąży jako frakcja mikrocząstek uwalnianych z komórek, takich jak płytki, monocyty i makrofagi lub adipocyty. Istnieje pogląd, że wysokie stężenie sCD36 w osoczu jest czynnikiem ryzyka wystąpienia przyspieszonej miażdżycy u chorych na cukrzycę typu 2, ponieważ wiąże się z rozwojem insulinooporności. Uważa się, że sCD36 mógłby stanowić marker przyspieszonej akumulacji lipidów w ścianie naczyń i związanego z nią ryzyka formowania blaszek miażdżycowych. Autorzy niniejszej pracy donosili już o związku polimorfizmu genu *CD36* z mniejszą grubością blaszki miażdżycowej, co sugeruje jego działanie ochronne przed rozwojem miażdżycy.

Cel: Celem niniejszej pracy było zbadanie związku między stężeniem w osoczu białka sCD36 a radiologicznymi parametrami postępu miażdżycy u pacjentów z chorobą wieńcową (CAD) rozpoznaną w młodym wieku.

Metody: Badaniami objęto 70 klinicznie stabilnych pacjentów z CAD rozpoznaną w młodym wieku. Grupę badaną stanowiło 52 mężczyzn w wieku poniżej 50 lat i 18 kobiet w wieku poniżej 55 lat. Próbkę krwi pobierano na czczo w celu oznaczenia stężenia glukozy w surowicy, profilu lipidów, stężenia apolipoprotein — ApoA1 i ApoB, Lp(a) oraz osoczowego stężenia białka sCD36. U każdego pacjenta zmierzono masę ciała, wzrost, obwód talii i bioder, skurczowe i rozkurczowe ciśnienie tętnicze oraz obliczono: wskaźnik masy ciała, wskaźnik talia–biodra i średnie ciśnienie tętnicze. Doplerowskie badanie ultrasonograficzne tętnic szyjnych i obwodowych przeprowadzono u wszystkich pacjentów. Grubość kompleksu intima–media (IMC) tętnicy szyjnej wspólnej i tętnic ramiennych, gęstość i grubość blaszki miażdżycowej w tętnicach szyjnych wspólnych i w rozwidleniu tętnic mierzono przy użyciu programu M'Ath. Stężenia w osoczu antygenu CD36 oznaczono za pomocą metody ELISA. Korelacje między zmiennymi ilościowymi a stężeniem sCD36 w osoczu oceniano współczynnikiem korelacji rang Spearmana (Rs), a związek między zmiennymi jakościowymi a stężeniem sCD36 w osoczu — za pomocą testu U Manna-Whitneya.

Wyniki: Nie zaobserwowano istotnych korelacji między osoczowym stężeniem sCD36 a radiologicznymi parametrami postępu miażdżycy, stwierdzono jedynie na granicy istotności negatywną korelację sCD36 z grubością IMC tętnicy ramiennej po stronie lewej, a w podgrupie kobiet istotną statystycznie negatywną korelację sCD36 z gęstością blaszki miażdżycowej prawej tętnicy szyjnej wspólnej. Okazało się, że pacjenci z niższym współczynnikiem kostka–ramię (< 0,9) charakteryzują się granicznie wyższym stężeniem sCD36 w osoczu.

Wnioski: Przedstawione wyniki nie wykazały silnych związków i nie dowodzą istotnej roli sCD36 w modulacji radiologicznych wskaźników postępu miażdżycy naczyń. Kolejne badania w celu oceny związku wysokich stężeń sCD36 w osoczu z ryzykiem niestabilności blaszki miażdżycowej u pacjentów z CAD rozpoznaną w młodym wieku należałoby przeprowadzić w grupie o znacznie większej liczebności.

Słowa kluczowe: osoczowy CD36, choroba wieńcowa, gęstość blaszki miażdżycowej, wskaźnik kostka–ramię

Kardiol Pol 2016; 74, 6: 570–575

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Praca wpłynęła: 08.04.2015 r. **Zaakceptowana do druku:** 22.10.2015 r. **Data publikacji AoP:** 27.11.2015 r.