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The relationship between the level of soluble CD40 ligand and angiographic extent and severity of coronary artery disease

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SOUHRN

Cíle: Podle dosavadních studií byla ateroskleróza považována za chronické zánětlivé onemocnění, přičemž složky imunitního systému se podílejí na aterogenezi. Systém receptoru CD40 a ligandu CD40 reguluje řadu fází hormonální a buněčné imunitní odpovědi. Zvláště solubilní ligand CD40 (sCD40) se uvolňuje z aktivovaných krevních destiček. Destičky se podílejí nejen na rozvoji trombózy, ale i na tvorbě aterosklerotických lézí a procesu restenózy. Cílem naší studie bylo zjistit, zda existuje vztah mezi hodnotami ligandu sCD40 a koronarograficky prokázaným rozsahem a závažností ischemické choroby srdeční (ICHS), a porovnat další rizikové faktory kardiovaskulárních onemocnění.
Metody: Do studie bylo zařazeno celkem 102 osob; z tohoto počtu bylo 37 pacientů s akutním koronárním syndromem (AKS), u 41 pacientů byla stanovena diagnóza stabilní anginy pectoris (SAP) a 24 jedinců tvořilo kontrolní skupinu. Při příjmu na koronární jednotku byly pacientům s AKS odebrány vzorky periferní žilní krve. U pacientů ze skupiny se SAP a u kontrolních osob se zdravými koronárními tepnami byly vzorky krve odebrány po koronarografickém vyšetření. U každého pacienta bylo vypočítáno Gensiniho skóre, kdy se u každé koronární stenózy určovalo skóre závažnosti podle stupně zúžení a jeho geografického významu.
Výsledky: Průměrné hodnoty ligandu sCD40 v séru byly statisticky významně vyšší u pacientů s AKS než u kontrol a pacientů se SAP ($p < 0{,}001$), přičemž rozdíl mezi skupinami kontrol a pacientů se SAP nebyl statisticky významný. Při srovnání podskupin s AKS nebyly průměrné hodnoty ligandu sCD40 statisticky významné. U pacientů s AKS ani se SAP nekorelovaly hodnoty ligandu sCD40 v séru s Gensiniho skóre ($p > 0{,}05$).
Závěr: Naše studie neprokázala vztah mezi hodnotami ligandu sCD40 a Gensiniho skóre u pacientů s různými klinickými podtypy ICHS. Ve skupině s AKS byly hodnoty ligandu sCD40 statisticky významně vyšší než v ostatních skupinách, ale v případě podskupin AKS nebyly statisticky významné rozdíly nalezeny. Z tohoto zjištění lze vyvozovat, že zvýšené hodnoty ligandu sCD40 by mohly sloužit jako ukazatel nestabilních plátů před rupturou a rozvojem nekrózy myokardu.

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ABSTRACT

Objectives: Previous studies have suggested that atherosclerosis is a chronic inflammatory disease and implicate components of the immune system in atherogenesis. The CD40 and CD40 ligand system regulates multiple phases of the humoral and cellular immune response. Soluble CD40 (sCD40) ligand especially releases from activated platelets. Platelets are involved not only in thrombosis, but also in atherosclerotic lesion formation and restenosis processes. The aim of our study is to evaluate whether there is a relationship between the level of sCD40 ligand and angiographic extent and severity of coronary artery disease (CAD) and to compare other cardiovascular risk factors.
Methods: 102 participants were included in our study. Among them, 37 patients constituted acute coronary syndrome (ACS) group, 41 patients were diagnosed as stable angina pectoris group (SAP), while 24 subjects served as control group. Peripheral venous blood samples were drawn at the Coronary Care Unit admission of ACS group patients. From SAP group patients and controls who have normal coronary arteries, blood samples collected after coronary angiography. The Gensini score was computed for each patient by assigning the severity score to each coronary stenosis in accordance with the degree of the vessel narrowing and its geographic importance.

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Results: Mean serum sCD40 ligand level was significantly higher in patients with ACS than the controls and SAP patients (p <0.001), there was no significant difference between SAP and control groups. Mean sCD40 ligand levels were not significantly different, when we compared ACS subgroups. Both in ACS and SAP patients, serum sCD40 ligand levels were not correlated with Gensini scores (p >0.05).
Conclusion: Our study doesn't show relation between sCD40 ligand levels and Gensini scores in patients with different clinical sub-types of CAD. In ACS group sCD40 ligand levels were significantly higher than in other groups, but there was no significant difference between ACS sub-groups. This finding suggests that increased sCD40 ligand levels can be used as a marker for determining the unstable plaque before ruptured and occurring myocardial necrosis.

Keywords:
Coronary artery disease
Gensini score
Soluble CD40 ligand

Introduction

Atherosclerosis is a systemic, chronic inflammatory disease and the primary cause of the cardiovascular disorders (CVD). Studies conducted in the last two decades have shown that inflammation and immune response play a crucial role in all stages of atherosclerosis, from its onset, progression and development of complications.[1,2]

C-reactive protein (CRP) is the most studied inflammation marker and it has been found to be valuable in determining both the risk of CVD in healthy individuals and recurrent ischemic events, mortality, and the need for revascularization after acute coronary events.[3] Similarly, soluble P selectin (sP-sel) reflecting platelet activation, and interleukin-6, a proinflammatory cytokine, are also known to be associated with the development of acute coronary events.[4,5] Since IL-6 and similar cytokines show circadian variation, CRP also increases in acute and chronic inflammatory conditions and can remain elevated for weeks after surgical interventions and trauma, they lose their importance as inflammatory markers. Recently, the most emphasized inflammatory marker is CD40/CD40 ligand system.

CD40 is a member of the tumor necrosis factor (TNF) receptor family and a cell surface protein synthesized in B lymphocytes, dendritic cells, monocytes, thymic epithelial cells, fibroblasts, endothelial cells, smooth muscle cells, and T lymphocytes. As for CD40 ligand is a protein that acts by binding to the CD40 receptor, has both a membrane-bound and soluble part. Membrane-bound CD40 ligand is synthesized mainly from CD4+ T lymphocytes, while soluble CD40 (sCD40) ligand primarily originates from activated platelets and has prothrombotic and proinflammatory effects that play a role in the pathogenesis of atherosclerosis and acute coronary syndromes (ACS).[6–8] The relationship between platelet activation and the severity of CAD has been demonstrated in various studies.[9,10] The release of soluble CD40 ligand from activated platelets raises the hypothesis that there may be a relationship between the prevalence of coronary artery disease and sCD40 levels.

The purpose of this study was to investigate the relationship of sCD40 ligand levels with the extent and severity of CAD and other cardiovascular risk factors in ACS and stable angina pectoris (SAP).

Methods

Study design and the selection of subjects

102 patients who underwent coronary angiography (CAG) in Istanbul University Cerrahpaşa Medical Faculty were included in the study. Of these, 37 patients were followed up with ACSs in the Coronary Care Unit and divided into three groups as ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina pectoris (USAP) according to ECG findings and cardiac enzyme levels. Forty one patients with exertional or stress induced angina pectoris that did not change the character and severity in the last two months were included in the SAP group. Twenty-four patients who were evaluated in cardiology outpatient clinics with various complaints and underwent CAG and were found to be normal constituted the control group.

Subjects with a history of myocardial infarction, heart failure, coronary artery disease and coronary artery revascularization, peripheral artery disease, active infection, chronic inflammatory disease, collagen tissue disease, malignancy and who used antiplatelets, anticoagulants, and statins were excluded from the study.

The study was conducted according to the principles of the Declaration of Helsinki and the study protocol was approved by the members of the Local Ethical Committee. Detailed written informed consent was obtained from all participants in advance.

Soluble CD40 ligand measurement

Blood samples for sCD40 ligand measurement were taken from patients in the ACS group at the time of admission to the hospital, before anticoagulant, antiaggregant treatment, and thrombolytic administration; while it was taken from the SAP patients after CAG, before any treatment and revascularization, and from the control group after CAG. 8 ml of blood from peripheral veins was centrifuged without any delay. Serum samples were stored in a –80 degrees cooler for simultaneous analysis of all patients. Measurements were made on ELH-CD40L-001 (RayBio human CD40L Elisa Kit) by ELISA method.

Coronary angiography evaluation

Coronary angiography was performed by experienced invasive cardiologists unaware of the study, using the standard Judkins technique. The number of involved vessels was calculated by looking at the presence of lesions causing ≥50% stenosis in the coronary arteries. Stenosis <50% was considered as non-critical coronary artery disease.

Gensini score was calculated by considering the degree of stenosis in the coronary arteries and its regional significance. 25%, 50%, 75%, 90%, 99% and 100% of the lumen diameter stenosis scores were given as 1, 2, 4, 8, 16 and 32, respectively. The coefficient of significance was given to the vascular regions in which stenosis was

detected, according to the functional importance of the myocardial area it supplies. For the left main coronary artery (LMCA), this coefficient is × 5; × 2.5 for left anterior descending artery (LAD) proximal; × 2.5 for proximal circumflex (Cx) artery; × 1.5 for anterior descending artery middle segment; × 1 for right coronary artery (RCA), distal anterior descending artery, first diagonal (D1) branch, posterolateral (PL) branch, and marginal branches; and × 0.5 for other side branches. For all arterial stenosis, the individual stenosis scores were multiplied by the functional significance coefficient and the Gensini score was calculated by summing the obtained numbers.[11]

Statistical analysis

SPSS (Statistical Package for Social Science) for Windows 16.0 statistical package program was used to evaluate the data. Data on continuous variables were expressed as mean ± standard deviation. ANOVA, Mann–Whitney U test, Kruskal–Wallis H test were used to compare numerical variables and Fisher exact test and Chi-square tests were used to compare categorical variables. Statistically, p <0.05 was considered significant. Correlation analysis was performed with Pearson analysis for continuous variables and with Spearman's correlation for categorical data. The correlation coefficient (r) was calculated.

Results

Thirty-seven ACS patients (mean age 59.49±11.34 years, male gender 81%), 41 SAP patients (mean age 58.73±9.83 years, male gender 61%), and 24 individuals without CAD (mean age 57.71±10.41, male gender 54.2%) participated in the study. There was no difference between the groups in terms of mean age, gender distribution, mean triglyceride levels, the history of HT and DM. Smoking rate and mean LDL levels were significantly higher in the ACS and SAP group compared to the control group (p <0.01). Mean HDL levels were found to be significantly lower in the ACS group than in the SAP and control groups (p <0.01). The hsCRP levels were significantly higher in the ACS and SAP groups than the control group, also significantly higher in ACS group than in SAP group. Gensini scores were detected significantly higher in the ACS group compared to the SAP group (Table 1). sCD40 ligand levels were found to be significantly increased in the ACS group than in the other groups (p <0.001) (Fig. 1).

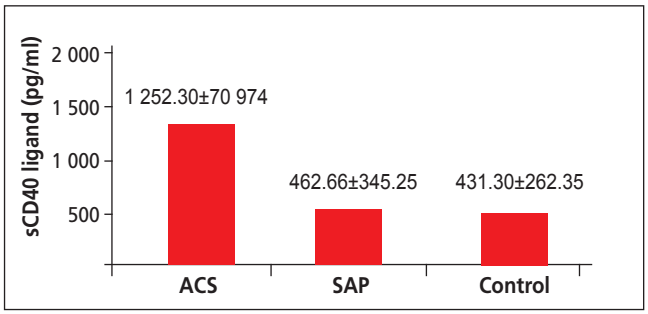


Fig. 1 – Graph showing comparison of sCD40 levels between groups. ACS – acute coronary syndrome; SAP – stable angina pectoris.

Analyses for patients in the ACS group

There were 37 patients in the ACS group. Considering the ECG findings and cardiac enzyme levels at admission and follow-up of the patients, 22 patients (59.46%) were defined as STEMI, 9 patients (24.32%) as NSTEMI, and 6 patients (16.22%) as USAP. The mean admission time of the patients after symptom onset was 8.6±6.4 hours. There was no statistically significant difference between ACS sub-groups in terms of demographic and laboratory findings (Table 2). In about 55% of the patients in the STEMI group, the lesion was on the anterior wall. When patients with anterior wall infarction and patients with non-anterior wall were compared, no significant difference was observed in terms of mean sCD40 ligand and hsCRP levels. The mean maximum troponin I level was found to be significantly higher in patients with anterior wall infarction. (Table 3).

The mean sCD40 ligand, hsCRP levels, and Gensini score did not differ significantly between genders, smokers and non-smokers, with and without DM and HT in ACS group (p >0.05).

Table 1 – Comparison of baseline clinical features and laboratory findings of the groups

Parameter	ACS (n = 37)	SAP (n = 41)	Control (n = 24)	*P*-value
Age	59.49±11.34	58.73±9.83	57.71±10.41	NS
Male, n (%)	30 (81.1)	25 (61)	13 (54.2)	NS
Hypertension, n (%)	20 (54.1)	26 (63.4)	16 (66.7)	NS
Diabetes mellitus, n (%)	6 (16.1)	14 (34.1)	4 (16.7)	NS
Smoking, n (%)	21 (56.8)	21 (51.2)	4 (16.7)	0.005
HDL (mg/dl)	37.86±14.93	43.95±7.43	46.83±7.16	0.004
LDL (mg/dl)	142±15.48	141.51±17.48	121.29±17.78	<0.001
Triglycerides (mg/dl)	177±34.7	193.66±30.3	183.67±20	NS
sCD40L (pg/ml)	**1 252.30±709.47**	462.66±345.25	431.30±262.35	**<0.001**
HsCRP (mg/L)	**18.62±5.77**	**15.47±7.15**	6.59±2.73	**<0.001**
Gensini score	54.60±39.89	37.37±35.97	–	**0.014**

HDL – high-density lipoprotein; HsCRP – high-sensitive C-reactive protein; LDL – low-density lipoprotein; NS – non-significant.

Table 2 – Clinical characteristics and laboratory findings of ACS sub-groups

Parameter	STEMI (n = 22)	NSTEMI (n = 9)	USAP (n = 6)	*P*-value
Age	58.22±11,92	63.66±10.01	57.83±11.28	NS
Male, n (%)	18 (81.8)	7 (77.8)	5 (83.3)	NS
Hypertension, n (%)	9 (40.9)	7 (77.8)	8 (66.7)	NS
Diabetes mellitus, n (%)	2 (9.1)	3 (33.3)	1 (16.7)	NS
Smoking, n (%)	14 (63.6)	4 (44.4)	3 (50)	NS
HDL (mg/dl)	38.72±17.9	38.66.±10.3	33.5±7.94	NS
LDL (mg/dl)	142.5±15,51	142.22±16.33	139.83±22.64	NS
Triglycerides (mg/dl)	173.63±37.88	178.55±29.58	187±32.73	NS
sCD40L (pg/ml)	1 371.61±846.89	1 049.40±445.39	1119.17±369.26	NS
HsCRP (mg/L)	18.04±6.53	19.65±5.28	19.21 ±3.52	NS
Gensini score	54.63±36.83	47.55±26.71	65.08±66.3	NS

HDL – high-density lipoprotein; HsCRP – high-sensitive C-reactive protein; LDL – low-density lipoprotein; NS – non-significant; NSTEMI – non-ST-elevation myocardial infarction; STEMI – ST-elevation myocardial infarction.

Table 3 – Correlation analyses in the ACS group

ACS group	sCD40 ligand		HsCRP		Gensini score	
	r	*p*	r	*p*	r	*p*
Age	–0.165	0.328	–0.309	0.062	–0.046	0.786
Hypertension	–0.249	0.137	–0.164	0.333	0.102	0.550
Diabetes mellitus	–0.027	0.872	–0.059	0.728	0.148	0.283
Smoking	0.051	0.764	0.148	0.381	–0.031	0.857
LDL (mg/dl)	–0.008	0.964	0.318	0.055	0.056	0.742
HDL (mg/dl)	**–0.331**	**0.034**	**–0.581**	**<0.001**	**–0.402**	**0.014**
TG (mg/dl)	0.276	0.098	**0.377**	**0.021**	0.111	0.513
Maximum troponin I level	0.222	0.187	-0.129	0.448	0.016	0.925
HsCRP (mg/L)	0.325	0.050	–	–	–	–
Gensini score	0.208	0.217	0.254	0.130	–	–

ACS – acute coronary syndrome; HDL – high-density lipoprotein; HsCRP – high-sensitive C-reactive protein; LDL – low-density lipoprotein; TG – triglycerides.

Table 4 – Comparison of demographic and clinical features according to median sCD40 ligand value in ACS group

sCD40 ligand	<1 115 pg/ml	≥1 115 pg/ml	*P*-value
	n (%)	n (%)	
Female, n (%) Male, n (%)	4 (57.1) 15 (50)	3 (42.9) 15 (50)	NS
Hypertension (+), n (%) (–), n (%)	11 (55) 8 (47)	9 (45) 9 (45)	NS
Diabetes mellitus (+), n (%) (–) n (%)	3 (50) 15 (48.3)	3 (50) 16 (52.7)	NS
Smoking (+), n (%) (–), n (%)	10 (47.6) 8 (50)	11 (52.4) 8 (50)	NS
STEMI, n (%) NSTEMI, n (%)	10 (45.6) 8 (53.3)	12 (54.4) 7 (46.7)	NS
Anterior MI, n (%) Non-anterior MI, n (%)	5 (41.7) 5 (50)	7 (58.3) 5 (50)	NS

NS – non-significant; NSTEMI – non-ST-elevation myocardial infarction; STEMI – ST-elevation myocardial infarction.

In the correlation analyses, there was no significant correlation between sCD40 ligand, Gensini score, and maximum troponin I levels. A weak positive correlation was observed between sCD40 ligand and hsCRP levels (r = 0.325, p = 0.05). HDL levels demonstrated a significant negative correlation with sCD40 ligand, hsCRP levels and Gensini score (r = –0.331, p = 0.034; r = –0.581, p <0.001; r = –0.402, p = 0.014, respectively). In addition, there was a significant positive correlation between hsCRP and triglyceride levels (r = 0.377, p = 0.021) (Table 4). sCD40 ligand, hsCRP levels, and Gensini score were not significantly correlated with HT, DM and smoking.

The median value of sCD40 ligand levels of 37 patients in the ACS group was determined as 1 115 pg/ml. Comparisons were made by dividing the patients into two groups according to whether they were below or above this value. In the evaluations made according to demographic features, ACS subgroups, lesion localization; no statistically significant difference was noted in the groups (Table 4).

Analyses for patients in the stable angina pectoris group

Forty-one patients were included in the SAP group. In the analyses performed in this group, a CD40 ligand levels showed a significant negative correlation with HDL and a significant positive correlation with smoking (r = –0.381, p = 0.018; r = 0.359, p = 0.021, respectively). There was a significant positive correlation between Gensini score and age, a significant negative correlation between Gensini score and HDL levels (r = 0.389, p = 0.012; r = –0.353, p = 0.024, respectively). No significant correlation was found among other parameters (Table 5).

There was no statistically significant difference in the mean sCD40L, hsCRP, and Gensini score between genders and between patients with and without DM in the SAP group (p >0.05). While no significant difference was observed between the hsCRP levels and Gensini scores between smokers and non-smokers, the mean sCD40 ligand levels were found to be significantly higher in smokers compared to non-smokers (590.82±358.99 vs 328.09±279.41, p = 0.013).

The median value of the sCD40 ligand levels in patients with SAP group was 438 pg/ml. Patients below and above this value were compared in terms of their clinical characteristics and no significant difference was found (Table 6).

Discussion

In our study designed on the basis of the hypothesis that sCD40 ligand levels, which are considered to be valuable in ACSs determining the risk of mortality and recurrent

Table 5 – Correlation analyses in the SAP group

SAP group	sCD40 ligand		HsCRP		Gensini score	
	r	*p*	r	*p*	r	*p*
Age	–0.107	0.506	0.022	0.890	**0.389**	**0.012**
Hypertension	0.081	0.613	0.307	0.051	–0.188	0.238
Diabetes mellitus	–0.126	0.432	0.013	0.934	–0.178	0.265
Smoking	**0.359**	**0.021**	-0.125	0.437	0.212	0.182
LDL (mg/dl)	–0.203	0.204	0.176	0.270	0.250	0.114
HDL (mg/dl)	**–0.381**	**0.018**	0.148	0.357	**–0.353**	**0.024**
TG (mg/dl)	–0.032	0.841	0.150	0.350	0.008	0.958
HsCRP (mg/L)	–0.040	0.803			–	–
Gensini score	–0.021	0.899	<0.001	0.999	–	–

HDL – high-density lipoprotein; HsCRP – high-sensitive C-reactive protein; LDL – low-density lipoprotein; SAP – stable angina pectoris; TG – triglycerides.

Table 6 – Comparison of the clinical features of the patients in the SAP group according to the median sCD40 ligand value

sCD40 ligand	<438 pg/ml (n = 20)	≥438 pg/ml (n = 21)	*P*-value
	n (%)	n (%)	
Female, n (%) Male, n (%)	10 (50) 10 (50)	6 (28.6) 15 (71.4)	NS
Diabetes mellitus (+), n (%) (–), n (%)	9 (45) 11 (55)	5 (23.8) 16 (76.2)	NS
Hypertension (+), n (%) (–), n (%)	13 (65) 7 (35)	13 (61.9) 8 (38.1)	NS
Smoking (+), n (%) (–), n (%)	7 (35) 13 (65)	14 (66.7) 7 (33.3)	NS

NS – non-significant.

ischemia, may be associated with the extent and severity of CAD, serum sCD40 ligand levels did not show a significant correlation with Gensini scores in both ACS and SAP groups.

Determining the fundamental role of inflammation in the process of atherosclerosis has been a milestone in understanding the pathogenesis of cardiovascular diseases, developing treatment approaches and identifying high risk patients.[12] Activated platelets have been shown to be important mediators in the formation and complication of atherosclerotic plaque.[13] This reveals the importance of sCD40 ligand, which is known to be mainly released from activated platelets, in the development of CAD and acute events. Several studies have shown that the sCD40 ligand is elevated in acute coronary syndromes and has prognostic significance.[14–16] Similarly, in our study, CD40 ligand levels were significantly higher in the ACS group and it was similar in SAP and control groups. Meanwhile CD40 ligand did not show significant association with Gensini score. On the contrary, Zhao et al. studied ACS patients and found a significant positive correlation between CD40 ligand levels and Gensini score.[17] However, only ACS patients were included in this study, and the differences between the ACS subgroups and different clinical forms of CAD were not examined. In a study by Fouad et al., similar to the results in our study, CD40 ligand level was found to be higher in the ACS group compared to the control and SAP groups, no significant difference was observed between the USAP and MI groups and complexity of culprit lesion and the number of coronary arteries with significant stenosis (≥50%) were not correlated with CD 40 ligand levels.[18] In our study, different from this study, the severity and extent of the coronary lesions were evaluated with the Gensini score, more participants were involved, and a more detailed analysis was made according to CV risk factors. It is salient that CD ligand levels were found to be similar to patients with myocardial necrosis and USAP patients. Because a noteworthy amount of acute myocardial infarctions develops from non-significant coronary lesions and about 25% of sudden cardiac deaths occur in patients who have no previous symptoms.[19–21] This reveals the importance of the characteristics of the plaque rather than the severity and the extent of the stenosis. In autopsy series, non-obstructive unstable plaques that are prone to rupture and develop acute vascular events are termed as "vulnerable plaques" and are characterized by a thin fibrous capsule, rich core lipid content, increased inflammatory activity, and vascular remodeling.[22,23] In recent years, cardiovascular research has focused on recognizing high-risk plaque before it ruptures and causes ACS. Considering that the current diagnostic and screening methods are not sufficient to identify patients at risk before the acute event, sCD40 ligand may be a considerable and useful marker at this point.

In comparisons with CV risk factors, a significant positive correlation was shown between smoking rate and sCD40 ligand levels in SAP group. It is known that smoking increases CD40 ligand synthesis on monocytes and CD40 ligand on platelets, and contributes to the inflammatory and thrombotic process by helping platelet-monocyte aggregation.[24] Since the sCD40 ligand levels were found to be significantly higher in smokers in our research, it can be thought that they contributed to this process not only by an increase in CD40 ligand synthesis on the surface of platelets, but also by causing platelet activation. In our evaluations with HDL, low levels of which are known to be associated with increased CV risk, a negative correlation was found with mean sCD40 ligand levels in both ACS and SAP groups. It is known that HDL contributes to the preservation of endothelial functions with antioxidant and antiatherogenic properties. It shows these effects by removing atherogenic lipids from the endothelium, regulating nitric oxide synthesis and changing the balance between prostacyclin and thromboxane A2 in favor of prostacyclin. HDL also impedes the activation of platelets by inhibition of platelet activating factor. This may explain its negative correlation with HDL, considering that a significant portion of the sCD40 ligand is released from activated platelets. In conclusion, our study could not demonstrate a relationship between sCD40 ligand levels and the angiographic extend and severity of coronary artery disease in patients with different clinical presentations. However, the fact that the mean sCD40 ligand levels in the USAP group were similar to those of STEMI and NSTEMI patients, and that there was no significant difference between the rates of patients below and above the median sCD40 ligand value, supports that sCD40 ligand may be a marker that can be used to detect unstable plaque before myocardial necrosis develops.

The major limitation of this study is the small number of patients in the ACS subgroups, although the total number of patients considered satisfactory. Since our study was not a follow-up study, the relationship of CD40 ligand with complications, restenosis, and recurrent cardiovascular events was not investigated.

Conflict of interest

The authors declared no conflict of interest.

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References

1. Bentzon JF, Otsuka F, Virmani R, et al. Mechanisms of plaque formation and rupture. Circ Res 2014;114:1852–1866.
2. Ross R. Atherosclerosis and inflamatory disease. N Engl J Med 1999;340:115–126.
3. Ridker PM, Buring JE, Cook NR, et al. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14719 initially healthy American women. Circulation 2003;107:391–397.
4. Ridker PM, Rifai N, Stamper MJ, et al. Plasma concentration of IL-6 and the risk of future myocardial infarction among apparently healthy men. Circulation 2000;101:1767–1772.
5. Ridker PM, Buring JE, Rifai N. Soluble P-selectin and the risk of future cardiovascular events. Circulation 2001;103:491–495.
6. Schönbeck U, Libby P. The CD40/CD154 receptor/ligand dyad. Cell Mol Life Sci 2001;58:4–43.
7. Mach F, Schonbeck U, Sukhova GK, et al. Functional CD40 ligand is expressed on human vascular endothelial cells, smooth muscle cells, and macrophages:implication for CD40–CD40 ligand signaling in atherosclerosis. Proc Natl Acad Sci USA 1997;94:1931–1936.
8. de Lemos JA, Zirlik A, Schönbeck U, et al. Associations between soluble CD40 ligand, atherosclerosis risk factors, and subclinical atherosclerosis: results from the Dallas Heart Study.

Arterioscler Thromb Vasc Biol 2005;25:2192–2196.
9. Ekici B, Erkan AF, Alhan A, et al. Is mean platelet volume associated with the angiographic severity of coronary artery disease? Kardiol Pol 2013;71:832–838.
10. Yao Y, Li X, Ji Q, et al. Interaction of Lipids, Mean Platelet Volume, and the Severity of Coronary Artery Disease Among Chinese Adults: A Mediation Analysis. Front Cardiovasc Med 2022;9:753171.
11. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol 1983;51:606.
12. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135–1143
13. Wang L, Tang C. Targeting Platelet in Atherosclerosis Plaque Formation: Current Knowledge and Future Perspectives. Int J Mol Sci 2020;21:9760.
14. Heeschen C, Dimmeler S, Hamm CW, et al.; CAPTURE Study Investigators. Soluble CD40 ligand in acute coronary syndromes. N Engl J Med 2003;348:1104–1111.
15. Garlichs CD, Eskafi S, Raaz D, et al. Patients with acute coronary syndromes express enhanced CD40 ligand/CD154 on platelets. Heart 2001;86:649–655.
16. Setianto BY, Hartopo AB, Achadiono DN, et al. Association between levels of circulating soluble CD40 ligand on admission and in-hospital events among acute coronary syndrome patients. Acta Med Indones 2011;43:82–87.
17. Zhao W, Zhang F, Li Z, et al. Soluble CD40 ligand is associated with angiographic severity of coronary artery disease in patients with acute coronary syndrome. Chin Med J (Engl) 2014;127:2218–2221.
18. Fouad HH, Al-Dera H, Bakhoum SW, et al. Levels of sCD40 ligand in chronic and acute coronary syndromes and its relation to angiographic extent of coronary arterial narrowing. Angiology 2010;61:567–573.
19. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988;12:56–62.
20. Shah PK. Mechanisms of plaque vulnerability and rupture. J Am Coll Cardiol 2003;41(4 Suppl S):15S–22S.
21. Mozaffarian D, Benjamin EJ, Go AS, et al; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. AHA statistical update. Heart disease and stroke statistics – 2016 update: a report from the American Heart Association. Circulation 2016;133:e38–e360.
22. Moreno PR. Vulnerable Plaque: Definition, Diagnosis, and Treatment. Cardiology Clinics 2010;28:1–30.
23. Virmani R, Kolodgie FD, Burke AP, et al. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 2000;20:1262–1275.
24. Michelson AD, Barnard MR, Kruger LA, et al. Circulating monocyte-platelet aggregates are a more sensitive marker of in vivo platelet activation than platelet surface P-selectin. Studies in baboons, human coronary intervention, and human acute myocardial infarction. Circulation 2001;104:1533–1537.