Soluble CD40 ligand release in patients with stable coronary artery disease during elective stent implantation: effect of drug-eluting stent over bare metal stent

Kararlı koroner arter hastalığı olanlarda elektif stent uygulması sırasında sCD40L salınımı: İlaç salınımlı stent ile çıplak metal stent etkisinin karşılaştırılması

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ABSTRACT

Objectives: We aimed to determine the effect of drug-eluting stent (DES) implantation on soluble CD40 ligand (sCD40L) levels in patients with stable coronary artery disease undergoing stent replacement.

Study design: Eighty-nine consecutive patients (33 women, 56 men; mean age 61±10 years) with stable coronary artery disease undergoing stent replacement were recruited. Pre- and post-procedural blood samples were collected for sCD40L analysis, and differences in plasma levels were calculated and expressed as delta sCD40L. Total size and length of implanted stents and pre- and post-dilatation procedures were recorded for each patient, for possible impact on sCD40L release. Patients were followed for one year following procedures for possible adverse cardiac events such as death, myocardial infarction and revascularization.

Results: Forty-nine patients received bare metal stent (BMS) and 40 patients received DES. There were no differences between BMS- and DES-implanted patients in terms of age, stent size and length, and delta sCD40L plasma levels. Delta sCD40L was correlated only with total implanted stent length (r=0.374, p<0.001). Delta sCD40L levels were divided into quartiles for better determination of the procedural parameters that are effective on biomarker release. Total stent length (p=0.008), stent size (p=0.038) and pre-dilatation procedure (p=0.034) were the statistically differing parameters between delta sCD40L quartiles. Although statistically non-significant, all three adverse events were observed in patients with the highest quartile (p=0.179).

Conclusion: Procedural sCD40L release did not differ between DES- and BMS-implanted stable coronary artery disease patients. Total implanted stent length, stent size and pre-dilatation procedure were the influential parameters on procedural sCD40L release.

ÖZET

Amaç: Kararlı koroner arter hastalığı olan kişilerde ilaç salınımlı stent (İSS) uygulamasının soluble CD40 ligand (sCD40L) seviyesi üzerine etkisi araştırıldı.

Çalışma planı: Stent uygulanan kararlı koroner arter hastalığı bulunan 89 ardışık hasta (33 kadın, 56 erkek; ortalama yaş 61±10 yıl) çalışmaya dahil edildi. Çıplak metal stent (ÇMS) veya İSS yerleştirilmesine hastanın klinik durumu ve lezyon özellikleri ile karar verildi. Plazma sCD40L seviyesi için işlem öncesi ve sonrası kan örnekleri alındı ve değerler arasındaki fark delta sCD40L olarak ifade edildi. Her bir hastaya yerleştirilen stentlerin toplam uzunluk ve genişliği ayrıca işlem öncesi ve sonrası dilatasyon uygulamaları kaydedildi. Hastalar işlem sonrası bir yıl takip edilerek ölüm, miyokart enfarktüsü ve revaskülarizasyondan oluşan olumsuz sonlanımlar gözlemlendi.

Bulgular: Kırk dokuz hastaya ÇMS, 40 hastaya ise İSS yerleştirildi. Her iki stent grubu arasında yaş, stent uzunluğu ve genişliği ve delta sCD40L plazma seviyesi açısından fark yoktu. Delta sCD40L sadece toplam stent uzunluğu ile ilişkiliydi (r=0.374, p<0.001). İşlemsel parametrelerin biyobelirteç salınımındaki etkilerinin daha iyi belirlenmesi için delta sCD40L değerleri çeyreklere bölünündü. Toplam stent uzunluğu (p=0.008), stent genişliği (p=0.038) ve öndilatasyon işlemi varlığı (p=0.034) sCD40L çeyrekleri arasında farklı parametreler olarak bulundu. İstatistiksel olarak anlamlılık sınırına ulaşmasa da tüm olumsuz sonlanımlar en yüksek çeyrekte gözlemlendi (p=0.179).

Sonuç: Kararlı koroner arter hastalığı grubunda ÇMS veya İSS uygulamasının işlemsel sCD40L salınımı üzerine etkisi yoktur. Toplam stent uzunluğu, stent genişliği ve öndilatasyon varlığı sCD40L salınımı ile ilişkili bulundu.

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Percutaneous coronary intervention (PCI) itself, which is used in the treatment of coronary artery disease (CAD), has an evident platelet-activating effect resulting in poor outcomes.[1,2] CD40 ligand (CD40L) is an established marker of platelet aggregation that plays an important role in thrombosis and plaque destabilization.[3,4] The soluble form of CD40, soluble CD40L (sCD40L), is released after platelet stimulation[5,6] and induces tissue factor expression on monocytes[7] and endothelial cells,[8] accelerating the inflammatory process and promoting coagulation. Mechanical endothelial injury is speculated as a reason for this early post-procedural elevation in CD40L levels.[9,10] Delayed arterial healing and impaired endothelial function are also suggested as possible mechanisms of adverse cardiac events following drug-eluting stent (DES) implantation.[11,12] However, the effect(s) of DES implantation on sCD40L levels in patients with stable CAD are not clear. In the present study, we investigated the impact of DES or bare metal stent (BMS) implantation on sCD40L release and outcomes in patients with stable CAD.

PATIENTS AND METHODS

Eighty-nine consecutive patients with stable CAD undergoing successful one or multivessel stent replacement were prospectively recruited. Successful procedure was defined as <20% residual stenosis, no procedural complications (dissection, abrupt vessel closure, side branch occlusion, no-reflow phenomenon, intracoronary thrombus, or distal embolization) and presence of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow. Death, myocardial infarction (MI) and urgent operation requirement were defined as clinical procedural complications.[13] A detailed history was obtained and thorough physical examination performed before the procedure. Patients with acute coronary syndrome, type C lesions in coronary arteries, renal failure, infectious diseases or inflammatory states, malignancy, and procedural failure were not included in the study. Simultaneous DES- and BMS-implanted patients were also excluded. All patients were given clopidogrel 300 mg loading dose 24 hours before the procedure and 75 mg/day maintenance, acetylsalicylic acid 300 mg/day, statins, and appropriate anti-hypertensive management. DES or BMS implantation was decided by the operator based on the lesion characteristics and the patient's clinical history. DESs, when used in appropriate patients, were sirolimus- and paclitaxel-eluting stents. Patients were followed for one year following procedures for possible adverse cardiac events determined as death, MI and revascularization.

Abbreviations:

BMS	*Bare metal stent*
CAD	*Coronary artery disease*
CD40L	*CD40 ligand*
DES	*Drug-eluting stent*
LAD	*Left anterior descending*
LCx	*Left circumflex artery*
MI	*Myocardial infarction*
PCI	*Percutaneous coronary intervention*
PTCA	*Percutaneous transluminal coronary angioplasty*
RCA	*Right coronary artery*
sCD40L	*Soluble CD40L*

Coronary angioplasty was performed according to a standard Judkins technique through a femoral approach. All patients were administered 100 IU/kg of unfractionated heparin intravenously. Stent implantation was performed with at least nominal balloon inflation pressure. Pre- and post-dilatation procedures were also performed if necessary. Total size and length of implanted stents and pre- and post-dilatation procedures were recorded for each patient, for possible impact on sCD40L release.

Blood samples were drawn from all patients, just before and 2 hours after the procedure. Tubes were centrifuged at 3500 rpm for 10 minutes. Plasma samples were stored at -20 °C until analyses. Samples were analyzed with commercially available Quantikine Human CD40 Ligand Immunoassay system (R&D Systems, Inc., USA), and results were expressed in pg/ml (assay range: 0.039-2.515 pg/ml). Pre- and post-procedural differences in sCD40L levels were calculated and expressed as delta sCD40L.

Informed written consent was obtained from each patient, and the study protocol was approved by the institutional local ethics review committees.

Statistical analysis

Statistical analyses were performed using a statistical software program (SPSS for Windows, version 15.0; SPSS Inc; Chicago, Illinois, USA). The obtained data were presented as mean ± SD, checked for normal distribution by Kolmogorov-Smirnov test and compared with unpaired Student t-test when the distribution appeared normal. Nonparametric test (Mann-Whitney U test) was used when there was non-normal distribution. Categorical data between two or more groups were compared by the χ^2 test. The correlations of continuous variables were analyzed by Pearson and ordinal variables by Spearman correlation analysis. Delta

sCD40L levels were divided into quartiles for better determination of the procedural parameters that are effective on biomarker release. A probability value of $p<0.05$ was considered as significant.

RESULTS

The study group included 33 women and 56 men (mean age: 61±10). Fifty-seven patients had hypertension (64%), 41 diabetes (46%) and 49 dyslipidemia (55%). Forty-nine patients received BMS and 40 patients received DES. Of the implanted DES, 16 were paclitaxel-eluting and 24 were sirolimus-eluting stents. Left anterior descending (LAD) was the target vessel in 40 patients, right coronary artery (RCA) in 23 patients and left circumflex artery (LCx) in 14 patients. Both LAD and RCA were stented consecutively in 3 patients, LAD and LCx in 5 patients and RCA and LCx in 4 patients during the same procedure. Median total implanted stent length was 27.5±15 mm (min-max: 9-100 mm) and stent width was 2.9±0.5 mm (min-max: 2.25-4.50 mm). Pre-dilatation procedure was performed in 47 patients (53%) and post-dilatation procedure was performed in 27 patients (30%). Plasma sCD40L levels were increased in all patients included in the study population following stent implantation procedures (Total study group sCD40L levels: Pre-procedural: 0.125±0.03 pg/ml, Post-procedural: 0.186±0.17 pg/ml, Delta: 0.06±0.05 pg/ml; Range of increase: Min-Max: 0.0010-0.34 pg/ml). There were no differences between BMS- and DES-implanted patients in terms of demographic and biochemical parameters, stent width and length, and delta sCD40L plasma levels. Pre- and post-dilatation procedures also did not differ between the two groups (Tables 1 and 2, Figure 1).

Delta sCD40L was correlated only with total implanted stent length ($r=0.374$, $p<0.001$) among the demographic, clinical and procedural parameters (Table 3). Delta sCD40L levels were divided into quartiles for better determination of the procedural parameters that are effective on biomarker release. Total stent length ($p=0.008$, Figure 2), stent width ($p=0.038$) and presence of pre-dilatation procedure ($p=0.034$) were the statistically differing parameters between delta sCD40L quartiles. Post-dilatation procedures were similar between sCD40L quartiles (Table 4).

Although presence of a pre-dilatation procedure was different between sCD40L quartiles, maxi-

Table 1. Baseline characteristics of the study groups

	BMS (n=49) (Median)			DES (n=40) (Median)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Gender (Female/Male)	20/29	41		13/27	32.5		0.510
Age (years)			60±10			62±9	0.473
Hypertension	31/18	63		25/15	62.5		0.941
Diabetes	23/26	47		18/22	45		0.855
Dyslipidemia	24/25	49		25/15	62.5		0.284
Smoking	7/42	14		7/33	17.5		0.773
Hemoglobin (g/dl)			13.8±1.8			14±1.9	0.414
Platelet (10^3 per mm^3)			255±79			254±59	0.821
Total cholesterol (mg/dl)			194±45			195±56	0.837
LDL (mg/dl)			124±38			127±43	0.586
HDL (mg/dl)			37±10			38±9	0.980
Triglyceride (mg/dl)			170±102			150±97	0.196
Creatinine (mg/dl)			0.93±0.23			0.96±0.23	0.631
CRP (mg/l)			1.27±1.2			1.05±1.1	0.652

Mann-Whitney U test was used due to non-normal distribution. Categorical data between two or more groups were compared by the χ^2 test.
BMS: Bare metal stent; DES: Drug-eluting stent; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; CRP: C-reactive protein.

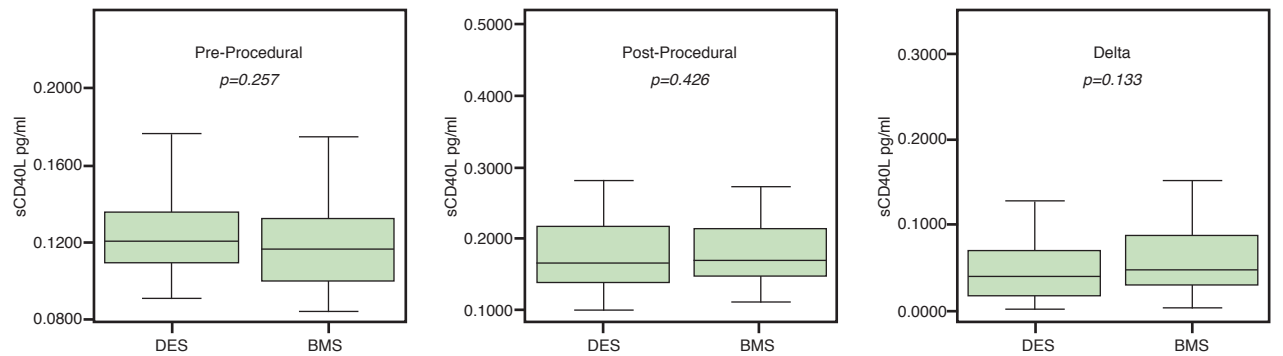

Figure 1. Box-plot graphics of pre-procedural, post-procedural and delta sCD40L levels between DES- and BMS-implanted patients.

Table 2. Biochemical and procedural differences between BMS- and DES-implanted patients

	BMS (n=49) (Median)			DES (n=40) (Median)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Total stent length (mm)			27.9±18			27.2±11	0.408
Stent width (mm)			3.4±1.2			3.2±1	0.248
Pre-sCD40L			0.124±0.032			0.127±0.029	0.257
Post-sCD40L			0.186±0.052			0.185±0.079	0.426
Delta sCD40L (pg/ml)			0.061±0.04			0.058±0.070	0.133
Pre-dilatation Y/N	28/21	57		19/21	47.5		0.399
Post-dilatation Y/N	11/38	22.5		16/24	40		0.104

Mann-Whitney U test was used due to non-normal distribution. BMS: Bare metal stent; DES: Drug-eluting stent; sCD40L: Soluble CD40L.

mal pre-dilatation pressures were similar (Q1: n=7; 12.3±1.8 mmHg, Q2: n=16; 12.6±1.6 mmHg, Q3: n=13; 12.8±1.3 mmHg, Q4: n=11; 12.2±1.2 mmHg, p=0.659). Post-dilatation pressures were also found similar between quartiles (Q1: n=0, Q2: n=5; 21.6±4.3 mmHg, Q3: n=5; 20.8±5.6 mmHg, Q4: n=4; 22.8±2.9 mmHg, p=0.919).

Adverse cardiac events occurred in 2 patients in the DES group and in 1 patient in the BMS group. Although statistically non-significant, all three adverse events occurred in the patients with the highest quartile of delta sCD40L (p=0.179).

DISCUSSION

Our study demonstrated a significant increase in sCD40L levels in all patients who underwent stent implantation. This increase was comparable between the BMS and DES groups. Parameters related to endothelial injury (implanted stent length, width and pre-dilatation procedure) were different between sCD40L quartiles.

Table 3. Correlation analysis between delta sCD40L and clinical, biochemical and procedural parameters

	R	*p*
Age	0.60	0.578
LDL	0.131	0.222
HDL	-0.052	0.632
Drug-eluting stent	0.160	0.135
Total stent length	0.374	**<0.001**
Pre-dilatation	-0.184	0.084
Post-dilatation	-0.201	0.059

LDL: Low-density lipoprotein; HDL: High-density lipoprotein; sCD40L: Soluble CD40L.

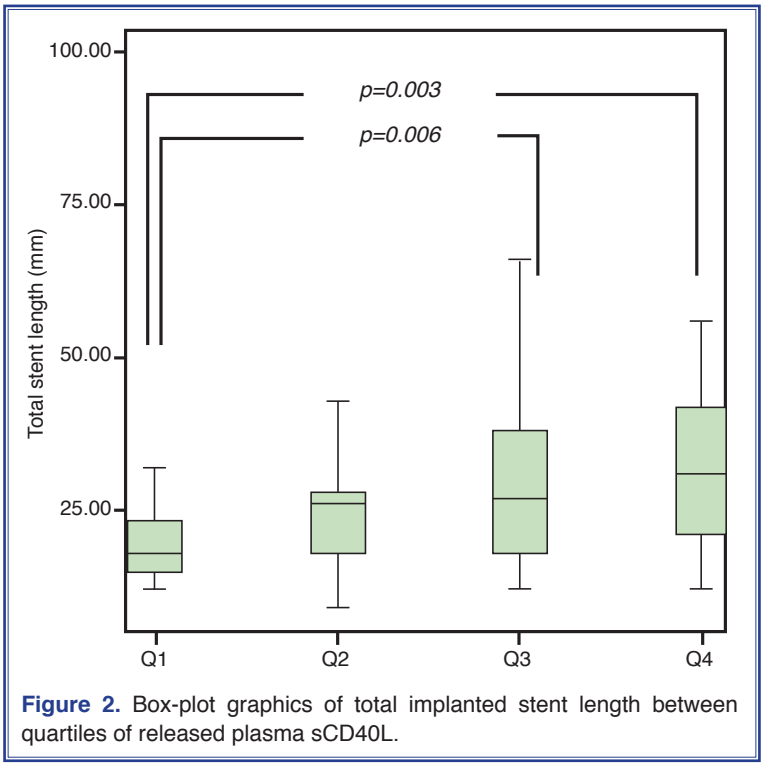

Figure 2. Box-plot graphics of total implanted stent length between quartiles of released plasma sCD40L.

Platelets are the main source of sCD40L, being responsible for >95% of circulating sCD40L levels.[14] Platelets express CD40L after stimulation with a wide range of platelet activators, such as thrombin and thrombin receptor agonists.[15] Patients with acute coronary syndrome have elevated levels of sCD40L, which is an independent predictor of death and recurrent MI in such patients.[14,16-18] However, the predictive value of sCD40L in patients with stable CAD has not been adequately clarified by large-scale clinical investigations.

The results of previous studies confirm that in stable patients, elevated levels of sCD40L do not predict CAD, ischemic stroke or recurrent coronary events and are not associated with a higher risk of future clinical events.[19-21]

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Table 4. Demographic and procedural differences between sCD40L quartiles

	0-25 Quartile (Median)			25-50 Quartile (Median)			50-75 Quartile (Median)			75-100 Quartile (Median)			*p*
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	
Gender (Female/Male)	6/17	26		6/16	27		12/14	46		9/9	50		0.230
Age (years)			61.3±12			59.3±9			60.7±9			62.5±11	0.856
Total stent length (mm)			19.1±5.6			20.6±6.7			31.3±18			29.8±12.5	0.008
Stent width (mm)			2.79±0.4			3.01±0.5			3.13±0.5			3.81±0.2	0.038
Pre-dilatation Y/N	7/16	30		16/6	73		13/13	50		11/7	61		0.034
Post-dilatation Y/N	3/20	13		8/14	36		9/17	35		7/11	39		0.214

Mann-Whitney U test was used due to non-normal distribution. Categorical data between two or more groups were compared by the χ^2 test.

(PTCA) itself is known to wreak damage on the endothelium, resulting in a platelet-activating effect with adhesion and aggregation of platelets.[22,23] sCD40L is a potential initiator of the inflammatory cascade after coronary intervention.[14,24] It is suggested that sCD40L is not a marker for chronic inflammation and coronary atherosclerosis but instead is an indicator of platelet activation.[19] The marked rise in sCD40L after mechanically induced plaque rupture by PTCA is speculated as a secondary phenomenon following endothelial injury.[25] It has been suggested that the degree of platelet activation may predict ischemic events, and up-regulation of the CD40 system may cause a local procoagulant and pro-inflammatory effect, which may increase the risk of restenosis and stent thrombosis.[1,2] In addition, elevated periprocedural levels of sCD40L have appeared to predict angiographic restenosis in patients who undergo coronary angioplasty and stent implantation.[26,27]

Sirolimus and paclitaxel are known as potent anti-inflammatory and immunomodulatory agents, and DES implantation was associated with reductions in periprocedural markers of inflammation and myonecrosis compared with BMS among acute coronary syndrome patients who underwent PCI.[28,29] However, it has been demonstrated that both sirolimus- and paclitaxel-eluting stents cause substantial impairment in arterial healing characterized by incomplete endothelialization and persistence of fibrin at autopsy when compared with BMS.[30,31] These observations explain the phenomenon of late stent thrombosis seen in DES-implanted patients. The acute effect of DES implantation on sCD40L release in stable patients, however, is not well defined.

While sCD40L release among DES- or BMS-implanted patients was similar in our study, stent length and width and existence of pre-dilatation procedure, which are the factors responsible for endothelial injury, were found as predictors of biomarker release. Aggarwal et al.[10] demonstrated that the number of implanted stents was one of the independent predictors of sCD40L release in patients who underwent stent implantation. The role of sCD40L release in these processes might be better understood in routine daily practice by considering the close relation between thrombogenic complications and the number of implanted stents and stent length. All three adverse events occurred in the highest quartile of delta sCD40L, indicating this relation between sCD40L release and cardiovascular complications.

Previous studies have revealed that anti-platelet therapy reduces sCD40L release, clarifying the success of these drugs in preventing thrombotic adverse events.[10,15,32] Our results also show similar biomarker release in both stent groups under the same doses of anti-platelet therapy.

The major limitation of the present study was the non-randomized recruitment of DES- or BMS- implanted patients; the effects of different doses of drugs on biomarker release was also not evaluated in this study and might be the subject of research for future studies. In addition, the inclusion of a greater number of participants in future studies might contribute to acquiring more accurate and definitive data. Finally, different drugs eluted from stent systems might influence the results of the study. Future studies comparing the effects of different types of DES on biomarker release might be useful.

In conclusion, procedural sCD40L release did not differ between DES- and BMS-implanted stable CAD patients. Total implanted stent length, stent size and pre-dilatation procedure were shown to be influential on procedural sCD40L release.

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Key words: Angioplasty, transluminal, percutaneous coronary; biological markers/blood; CD40 ligand/blood; coronary artery disease/blood; drug-eluting stents; platelet aggregation inhibitors; stents.

Anahtar sözcükler: Anjiyoplasti, transluminal, perkütan, koroner; biyolojik belirteç/kan; CD40 ligand/kan; koroner arter hastalığı/kan/ilaç tedavisi; ilaç salınımlı stent; trombosit agregasyon inhibitörü; stentler.