Usefulness of Circulating Decoy Receptor 3 in Predicting Coronary Artery Disease Severity and Future Major Adverse Cardiovascular Events in Patients With Multivessel Coronary Artery Disease

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Decoy receptor 3 (DcR3), a member of the tumor necrosis factor receptor superfamily, is an antiapoptotic soluble receptor considered to play an important role in immune modulation and has pro-inflammatory functions. This study was designed to test whether circulating DcR3 levels are associated with coronary artery disease (CAD) severity and predict future major adverse cardiovascular events (MACEs) in patients with CAD. Circulating DcR3 levels and the Syntax score (SXscore) were determined in patients with multivessel CAD. The primary end point was the MACE within 12 months. In total, 152 consecutive patients with angiographically confirmed multivessel CAD who had received percutaneous coronary intervention were enrolled and were divided into 3 groups according to CAD lesion severity. Group 1 was defined as low SXscore (≤13), group 2 as intermediate SXscore (>13 and ≤22), and group 3 as high SXscore (>22). DcR3 levels were significantly higher in the high SXscore group than the other 2 groups (13,602 ± 7,256 vs 8,025 ± 7,789 vs 4,637 ± 4,403 pg/ml, p <0.001). By multivariate analysis, circulating DcR3 levels were identified as an independent predictor for high SXscore (adjusted odds ratio 1.15, 95% confidence interval 1.09 to 1.21; p <0.001). The Kaplan-Meier analysis showed that increased circulating DcR3 levels are associated with enhanced 1-year MACE in patients with multivessel CAD (log-rank p <0.001). In conclusion, increased circulating DcR3 levels are associated with CAD severity and predict future MACE in patients with multivessel CAD. **(Am J Cardiol 2015;116:1028−1033)**

Decoy receptor 3 (DcR3), also known as tumor necrosis factor receptor superfamily (TNFRSF) 6b, is a soluble receptor and is considered an immune modulator, based on its neutralizing effects on Fas ligand (FasL), LIGHT, and TNF-like cytokine 1A (TL1A). Recent study has suggested that DcR3 can increase monocyte adhesion to endothelial cells and reduce phagocytic activity of macrophages toward apoptotic bodies and immune complexes.[1] The impaired phagocytosis of apoptotic cells by macrophages may lead to the progression of atherosclerosis in human atherosclerotic plaques.[2] Kidney function as measured by glomerular filtration rate was found to be inversely correlated with the complexity and severity of CAD,[3] which could be quantified by Syntax score (SXscore), a comprehensive anatomic scoring system based on the coronary angiogram.[4] Recent study has shown that DcR3 levels can independently predict cardiovascular and all-cause mortality in patients with end-stage renal disease,[5] who are prone to develop more advanced atherosclerotic CAD. However, whether circulating DcR3 level is associated with coronary atherosclerotic lesion severity and predicts future cardiovascular events in patients with advanced atherosclerotic CAD who underwent percutaneous coronary intervention (PCI) has not been explored. Based on these findings, we conducted a longitudinal analysis to test the hypothesis that DcR3 levels are associated with the severity of CAD and predict future cardiovascular events in patients with multivessel CAD who underwent PCI.

Methods

This study enrolled consecutive patients who were admitted to a tertiary medical referral center for PCI from

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2012 to June 2013, with stable CAD and angiographically confirmed multivessel disease, defined as stenosis of ≥50% in ≥2 major epicardial vessels involving ≥2 separate coronary artery territories. Before enrollment, a detailed review of each patient's chart was conducted to gather data on medications, smoking status, and risk factors for CAD, such as age, hypertension, diabetes mellitus (DM), dyslipidemia, chronic kidney disease (CKD), and other co-morbidities. Smokers were classified as former only if they had successfully abstained for >6 months. Hypertension was defined as a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or use of antihypertensive treatment. DM was defined as fasting plasma glucose ≥126 mg/dl or use of hypoglycemic agents. CKD was defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2. Patients were excluded if the coronary anatomy was not suitable for PCI or if emergent coronary artery bypass grafting (CABG) surgery was required. Patients with acute coronary syndrome or acute myocardial infarction (MI) who required primary PCI were also excluded. The study was approved by the research ethics committee of Taipei Veterans General Hospital (VGHIRB No.: 2012-03-001AC and 2014-04-005CC), and all participants provided their written informed consent.

After an overnight fast ≥8 hours, blood samples were obtained from all patients. Serum levels of creatinine and lipid profiles including triglycerides, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were measured using a Hitachi 7600 autoanalyzer (Hitachi Ltd, Tokyo, Japan). Serum levels of DcR3 (Biovendor, Modrice, Czech Republic) were measured using commercially available enzyme-linked immunosorbent assay (ELISA, BioLegend Inc, San Diego, CA) kits according to the manufacturer's instructions. Serum high-sensitivity C-reactive protein (hs-CRP) levels were measured using an immunoturbidimetric assay and rate nephelometry (IMMAGE; Beckman Coulter, Galway, Ireland).

Two expert angiographers, blind to the patient's clinical and laboratory data, independently reviewed the coronary angiography. Each coronary lesion with a diameter stenosis of ≥50%, in vessels of ≥1.5 mm, was scored. The latest updated version of the calculation algorithm found online was used for the calculation of the SXscore (*http://www.Syntaxscore.com*).[4] The patients were then divided into different groups according to their SXscore.

All patients were stratified into 3 groups according to their SXscore values in tertile. Patients with SXscore >22 (highest tertile) were defined as the high SXscore group (n = 50, 33%), those with SXscore ≤13 (lowest tertile) as the low SXscore group (n = 51, 34%), and those with SXscore >13 and ≤22 as the intermediate-SXscore group (n = 51, 34%).

All patients included in the study were followed up for 12 months or until the occurrence of a major adverse cardiovascular event (MACE). The study end point was the MACE, defined by a composite of clinical events including death, fatal or nonfatal MI, ischemic stroke, and target vessel revascularization (TVR). All participants were contacted by telephone periodically and their medical records were followed up regularly. No patients dropped out of the study, and all occurrences of adverse events were recorded. Nonfatal MI was defined as an increase of cardiac troponin I with ischemic symptoms and/or characteristic electrocardiographic changes. Ischemic stroke was defined as the presence of a new neurologic deficit lasting for ≥24 hours with definite evidence of a cerebrovascular accident verified by either magnetic resonance imaging or computed tomography. TVR was defined as any clinically driven repeat

Table 1
Baseline characteristics of patients with low, medium and high Syntax score

Variables	Syntax Score			P value
	≤13 (n = 51)	>13 and ≤22 (n = 51)	>22 (n = 50)	
Age (years)	72.0 ± 10.4	72.9 ± 13.0	72.7 ± 11.8	0.933
Male	37 (73%)	37 (73%)	36 (72%)	0.997
Smoker	12 (24%)	12 (24%)	10 (20%)	0.887
Hypertension	39 (77%)	40 (78%)	35 (70%)	0.593
Diabetes mellitus	26 (51%)	24 (47%)	31 (62%)	0.297
Previous MI	10 (20%)	25 (49%)	20 (40%)	0.007
Previous CVA	9 (18%)	7 (14%)	9 (18%)	0.812
Heart failure	23 (45%)	19 (37%)	23 (46%)	0.619
Atrial fibrillation	10 (20%)	9 (18%)	13 (26%)	0.561
Chronic kidney disease	24 (47%)	26 (51%)	25 (50%)	0.919
Lipid profiles (mg/dl)				
Triglycerides	118.9 ± 61.1	107.6 ± 48.9	118.3 ± 72.0	0.599
Total cholesterol	148.3 ± 54.5	153.4 ± 54.4	167.9 ± 45.9	0.147
HDL-C	40.1 ± 10.9	40.8 ± 12.5	45.1 ± 11.7	0.089
LDL-C	80.9 ± 43.4	85.2 ± 53.4	98.7 ± 46.9	0.158
Creatinine (mg/dl)	1.56 ± 1.32	2.04 ± 2.25	1.99 ± 2.42	0.431
DcR3 levels (pg/dL)	4637 ± 4403	8025 ± 7789	13602 ± 7256	<0.001
Syntax score	9.4 ± 8.5	18.0 ± 2.6	30.1 ± 5.9	<0.001
Hs-CRP (mg/L)	0.85 ± 1.75	1.62 ± 2.39	1.59 ± 3.56	0.261

CVA = cerebrovascular accident; DcR3 = decoy receptor 3; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction.

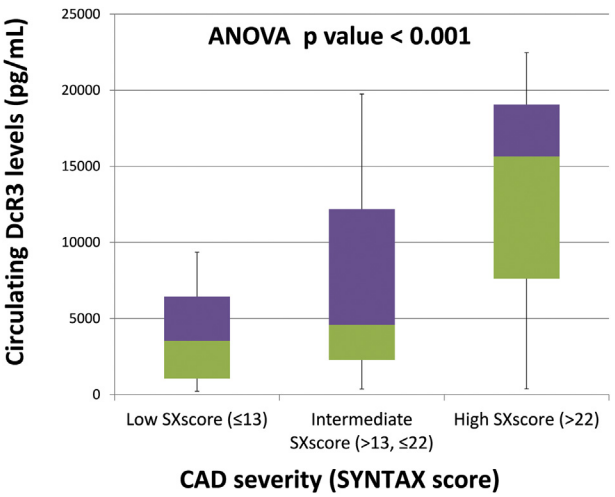

Figure 1. Circulating DcR3 levels among low, intermediate, and high SYNTAX score groups. The box-and-whisker plot shows the minimum, maximum, median, the first quartile, and the third quartile of the DcR3 values. ANOVA = analysis of variance.