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Plasma interleukin-27 levels in patients with coronary artery disease

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Abstract

Interleukin (IL)-27, one of cytokines in the IL-12 family, is considered to have both pro- and anti-inflammatory properties. However, blood IL-27 levels in coronary artery disease (CAD) have not been fully elucidated yet. This cross-sectional study was done to elucidate the association between blood IL-27 levels and CAD.

We investigated plasma IL-27 and high-sensitivity C-reactive protein (hsCRP) levels in 274 consecutive patients who underwent elective coronary angiography for suspected CAD. CAD was present in 177 patients [30 acute coronary syndrome (ACS) and 147 stable CAD]. Compared with 97 patients without CAD, 177 patients with CAD had higher IL-27 (median 0.26 vs 0.22 ng/mL, $P < .05$) and higher hsCRP (0.98 vs 0.41 mg/L, $P < .001$) levels. However, there was no significant difference in IL-27 levels among 3 groups of ACS, stable CAD, and CAD(-) (0.26, 0.25, and 0.22 ng/mL), whereas hsCRP levels were significantly higher in ACS and stable CAD than in CAD(-) (2.09, 0.91 vs 0.41 mg/L, $P < .001$) and were highest in ACS. IL-27 levels tended to increase with the number of >50% stenotic coronary vessels: 0.22 in CAD(-), 0.22 in 1-vessel disease, 0.31 in 2-vessel disease, and 0.27 ng/mL in 3-vessel disease ($P < .05$). A stepwise increase in hsCRP levels was also found: 0.41 in CAD(-), 0.75 in 1-vessel, 1.05 in 2-vessel, and 1.85 mg/L in 3-vessel disease ($P < .001$). Plasma hsCRP levels significantly ($r = 0.35$), but IL-27 levels weakly ($r = 0.15$), correlated with the number of stenotic coronary segments. In multivariate analysis, both IL-27 and hsCRP levels were independent factors associated with CAD. However, hsCRP, but not IL-27, was also a factor for ACS.

While plasma IL-27 levels were high in patients with CAD, these levels were an independent factor for only CAD, not ACS, and weakly correlated with the severity of CAD. Our results suggest that IL-27 is unlikely to be a good biomarker reflecting the severity of CAD or the presence of ACS, or to play a major role in the progression of CAD.

Abbreviations: ACS = acute coronary syndrome, CAD = coronary artery disease, ELISA = enzyme-linked immunosorbent assay, hsCRP = high-sensitivity C-reactive protein, IFN = interferon, IL = interleukin, MI = myocardial infarction, NSTEMI = non-ST elevation MI, STEMI = ST-segment elevation MI, Th = T-helper, UAP = unstable angina.

Keywords: coronary artery disease, c-reactive protein, inflammation, interleukin-27

1. Introduction

Atherosclerotic diseases, such as coronary artery disease (CAD), are recognized to be chronic inflammatory diseases, and the imbalance of pro- and anti-inflammatory cytokines plays an important role in atherosclerosis.[1] T-helper (Th) cells differentiate into Th1 and Th2 subsets. Th1 cells secrete pro-inflammatory cytokines, including interferon (IFN)-γ and interleukin (IL)-2, and play a major role in cellular immunity, whereas Th2 cells secrete IL-4 and IL-10 and promote humoral immunity.[2] Thus, the upregulation of Th1-related pro-inflammatory response and the downregulation of Th2-related anti-inflammatory response leads to the progression of atherosclerosis.[2,3]

IL-27, one of cytokines in the IL-12 family, is a heterodimeric cytokine composed of EBI3 and p28 protein.[4] Notably, IL-27 is considered to have dual functions in regulating the immune responses, with both pro- and ant-inflammatory properties.[5] IL-27 promotes early Th1 differentiation via Signal Transducers and Activators of Transcription-1-mediated T-bet activation[6] and induces IFN-γ, IL-1, and tumor necrosis factor (TNF)-α production,[4,7,8] but IL-27 suppresses Th2 differentiation and Th2 cytokine production.[9] In contrast, IL-27 suppresses Th17 differentiation and IL-2 production[5] and induces anti-inflammatory IL-10 production by T cells.[10] However, the role of IL-27 in promoting or suppressing inflammation may vary among diseases.[11] For example, IL-27 may promote inflammation in crescentic glomerulonephritis and systemic sclerosis.[12,13] IL-27 receptor-deficient mice developed less severe proteoglycan-

Editor: Yuan Lin.

Funding/support: Financial funding of this study was provided in part by Daiichi Sankyo Co. and Pfizer Japan Inc., but these sponsors had no role in the design, analysis, and interpretation of the study.

All authors declare no conflict of interest to disclose.

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Medicine (2017) 96:43(e8260)

Received: 2 June 2017 / Received in final form: 11 September 2017 / Accepted: 18 September 2017

http://dx.doi.org/10.1097/MD.0000000000008260

induced arthritis.[14] In contrast, IL-27 suppresses inflammation in autoimmune encephalomyelitis and uveitis.[15,16]

Although cytokines are known to play an important role in atherosclerosis, the role of IL-27 has not been clarified.[3] Kempe et al[17] investigated IL-27 expression in carotid endarterectomy specimens and showed its expression of macrophages and endothelial and smooth muscle cells in atherosclerotic lesions. They also reported cultured aortic smooth muscle cells to upregulate IL-27 expression in response to IFN-γ and TNF-α. Qiu et al[18] demonstrated that IL-27 enhanced TNF-α mediated upregulation of adhesion molecules and pro-inflammatory IL-6 in cultured coronary artery endothelial cells. High mRNA expressions of IL-27 as well as IL-6 and TNF-α in blood monocytes were also reported in patients with acute myocardial infarction (MI).[19] These findings suggest a possible role of IL-27 in atherogenesis. However, Koltsova et al[20] demonstrated that Ldlr-/- mice transplanted with IL-27 receptor-/- bone marrow developed large atherosclerotic lesions. Hirase et al[21] also reported that IL-27 deficient mice had enhanced atherosclerosis with macrophage activation and that recombinant IL-27 treatment suppressed atherosclerosis. IL-27 may thus play an inhibitory role in atherosclerosis. Hence, the role of IL-27 in atherosclerosis remains controversial, and studies showing blood IL-27 levels in patients with CAD are scarce.[11,22,23] This cross-sectional study was done to elucidate the associations between blood IL-27 levels and the presence and severity of CAD. We measured plasma levels of IL-27 as well as high-sensitivity C-reactive protein (hsCRP), which is the most commonly used inflammatory biomarker, in 274 patients undergoing elective coronary angiography.

2. Material and methods

2.1. Study patients

We investigated plasma levels of IL-27 and hsCRP in 274 consecutive patients who underwent elective coronary angiography for suspected CAD at Tokyo Medical Center from July 2008 to December 2012. CAD was defined as at least 1 coronary artery having >50% luminal diameter stenosis. Acute coronary syndrome (ACS) was classified into 2 groups [acute MI and unstable angina (UAP)]. Acute MI was defined as the presence of ischemic symptoms and elevated Troponin T levels by the Third Universal Definition of MI[24] and was classified into ST-segment elevation MI (STEMI) and non-ST elevation MI (NSTEMI). UAP was defined as ischemic symptoms at rest with ST-T changes, so-called class III according to Braunwald classification.[25] Of the 274 study patients, CAD was found in 177 patients, of whom 30 had ACS (15 NSTEMI and 15 UAP) and 147 had stable CAD. Our study was approved by the institutional ethics committee of our hospital (approval no. R07-054/15-056). After written informed consent was obtained from the study patients, overnight fasting blood samples were taken on the morning of the day that coronary angiography was performed. As patients with STEMI commonly undergo urgent coronary angiography, no patient with STEMI was included in this study. Patients with a history of percutaneous coronary intervention or cardiac surgery were excluded. Patients with valvular heart disease, malignant disease, or inflammatory disease were also excluded from this study. Hypertension was defined as a blood pressure of ≥140/90 mm Hg or on drugs; 165 (60%) patients were taking anti-hypertensive drugs. Hyperlipidemia was defined as a low-density lipoprotein (LDL)-cholesterol level of >140 mg/dL or on drugs; 107 (39%) patients were taking statins. Diabetes mellitus (DM, a fasting plasma glucose level of ≥126 mg/dL or on treatment) was present in 86 (31%) patients, and 102 (37%) were smokers (≥10 pack-years).

2.2. Measurements of plasma IL-27 and hsCRP levels

Blood samples were collected in EDTA-containing tubes, and the plasma was stored at –80°C. Plasma IL-27 levels were measured by an enzyme-linked immunosorbent assay (ELISA) using a commercially available kit (LEGEND MAX Human IL-27 ELISA Kit; BioLegend, San Diego, CA) at Ochanomizu University in accordance with the manufacturer's instructions. The minimum level detected by this assay was 0.01 ng/mL. The intra-assay and inter-assay coefficients of variation were <6.0% and <5.5%, respectively. Plasma hsCRP levels were measured by a BNII nephelometer (Dade Behring, Tokyo, Japan).

2.3. Coronary angiography

Coronary angiograms were recorded on a cardiac cineangiogram system (Philips Electronics Japan, Tokyo, Japan). CAD was defined as at least 1 coronary artery having >50% luminal diameter stenosis. The severity of coronary atherosclerosis was represented as the numbers of >50% stenotic vessels and >50% stenotic segments. The Gensini score[26] was also calculated as follows: the degree of stenosis in each segment was scored from 1 to 32 (1, ≤25%; 2, 26–50%; 4, 51–75%; 8, 76–90%; 16, >90% stenosis; 32, 100% occlusion) and then were multiplied by a factor depending on the functional significance of the area perfused by the stenotic segment. A total of 29 coronary artery segments were defined according to the Coronary Artery Surgery Study classification. All coronary angiograms were evaluated by a single cardiologist (Y.M.), who was blinded to the clinical and laboratory data.

2.4. Statistical analysis

The statistical analysis was performed using the SPSS, version 20.0, software (IBM, Tokyo, Japan). Differences between 2 groups were evaluated by the unpaired *t* test for parametric variables, by the Mann–Whitney *U* test for nonparametric variables, and by the Chi-squared test for categorical variables. Differences among 3 or more groups were evaluated by an analysis of variance with Scheffe test for parametric variables and by the Kruskal–Wallis test with the Steel–Dwass test for nonparametric variables. Correlations between IL-27 or hsCRP levels and the severity of coronary atherosclerosis were evaluated by Spearman rank correlation test. To determine the cut-off point of IL-27 levels for CAD, a relative cumulative frequency distribution curve was created, and the optimal cut-off point was determined to be 0.25 ng/mL. Regarding the cut-off point of hsCRP levels, the previously reported cut-off point of 1.0 mg/L for CAD or cardiovascular events was used.[27,28] Forward stepwise multiple logistic regression analysis was used to determine independent associations between IL-27 or hsCRP levels and CAD. A *P* value of <.05 was considered to be statistically significant. The results are presented as the mean ± SD or the median value.

3. Results

Of the 274 study patients, CAD was found in 177 patients, of whom 30 had ACS (15 NSTEMI and 15 UAP) and 147 had stable CAD. Compared with 97 patients without CAD, 177 patients with CAD were older and had a male predominance and a higher

Table 1

Clinical characteristics and plasma IL-27 and hsCRP levels.

	CAD (-) (n=97)	*P* CAD (-) vs CAD	CAD (n=177)	CAD (-) vs stable CAD	Stable CAD (n=147)	Stable CAD vs ACS	ACS (n=30)	CAD (-) vs ACS
Age, y	64±11	<.001	70±10	<.001	70±10	NS	70±9	<.01
Gender (male)	63 (65%)	<.05	138 (78%)	<.05	114 (78%)	NS	24 (80%)	NS
Hypertension	54 (56%)	<.005	134 (76%)	<.001	115 (78%)	NS	19 (63%)	NS
SBP, mm Hg	129±18	NS	134±26	NS	133±26	NS	143±22	<.001
Diabetes mellitus	19 (20%)	<.005	67 (38%)	<.005	58 (39%)	NS	9 (30%)	NS
Smoking	32 (33%)	NS	70 (40%)	NS	59 (40%)	NS	11 (37%)	NS
Hyperlipidemia	46 (47%)	NS	102 (58%)	NS	87 (59%)	NS	15 (50%)	NS
Statin	30 (31%)	NS	77 (44%)	NS	65 (44%)	NS	12 (40%)	NS
LDL-C, mg/dL	110±30	<.05	120±36	<.05	120±37	NS	117±31	NS
HDL-C, mg/dL	58±15	<.001	51±13	<.005	52±14	NS	48±12	<.01
hsCRP levels, mg/L	0.41 [0.22, 0.83]	<.001	0.98 [0.43, 2.62]	<.05	0.91 [0.41, 2.15]	<.05	2.09 [0.69, 6.03]	<.05
IL-27 levels, ng/mL	0.22 [0.15, 0.32]	<.05	0.26 [0.17, 0.39]	NS	0.25 [0.17, 0.39]	NS	0.26 [0.18, 0.38]	NS

Data are the mean±SD or the number (%) of patients, except for hsCRP and IL-27 levels, which are presented as the median value and interquartile range.
ACS = acute coronary syndrome, CAD = coronary artery disease, HDL-C, high-density lipoprotein cholesterol, hsCRP = high-sensitivity C-reactive protein, IL = interleukin, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure.

prevalence of hypertension and DM, and higher LDL-cholesterol levels and lower high-density lipoprotein (HDL)-cholesterol levels (Table 1). However, IL-27 levels did not differ between 86 patients with DM and 188 without DM (median 0.24 vs 0.23 ng/mL), but hsCRP levels were higher in patients with DM than without DM (0.92 vs 0.55 mg/L, $P<.02$). Compared with patients without CAD, those with CAD had higher IL-27 (0.26 vs 0.22 ng/mL, $P<.05$) and higher hsCRP (0.98 vs 0.41 mg/L, $P<.001$) levels (Table 1, Fig. 1). However, IL-27 levels did not differ among 3 groups of ACS, stable CAD, and CAD(-) (0.26, 0.25, and 0.22 ng/mL) (Fig. 2), whereas hsCRP levels were significantly higher in ACS and stable CAD than in CAD (-) (2.09, 0.91 vs 0.41 mg/L, $P<.001$) and were highest in ACS (Fig. 2). Between patients with NSTEMI and UAP, there was no significant difference in IL-27 (0.24 vs 0.27 ng/mL) and hsCRP (3.21 vs 1.36 mg/L) levels.

Of the 177 CAD patients, 66 had 1-vessel, 53 had 2-vessel, and 58 had 3-vessel disease. IL-27 levels tended to increase with the number of >50% stenotic coronary vessels: 0.22 in CAD (-), 0.22 in 1-vessel, 0.31 in 2-vessel, and 0.27 ng/mL in 3-vessel disease ($P<.05$). A stepwise increase in hsCRP levels was also found: 0.41 in CAD (-), 0.75 in 1-vessel, 1.05 in 2-vessel, and 1.85 mg/L in 3-vessel disease ($P<.001$); hsCRP levels were highest in 3-vessel disease (Fig. 3). Moreover, IL-27 levels weakly correlated ($rs=0.15$ and $rs=0.16$, $P<.02$) and hsCRP levels significantly correlated ($rs=0.35$ and $rs=0.31$, $P<.001$) with the number of >50% stenotic coronary segments and the Gensini score, respectively. However, no significant correlation was found between IL-27 and hsCRP levels.

To elucidate independent associations between IL-27 or hsCRP levels and CAD, variables (age, gender, hypertension, hyperlipidemia, statin use, diabetes, smoking, and IL-27 and hsCRP levels) were entered into a multiple logistic regression model. Both IL-27 and hsCRP levels as well as age, gender, hypertension, and hyperlipidemia were independent factors associated with CAD. The odds ratios for CAD were 1.83 [95% confidence interval (95% CI)=1.01–3.32, $P<.05$] for high IL-27 level (>0.25 ng/mL) and 3.40 (95% CI=1.78–6.50, $P<.001$) for high

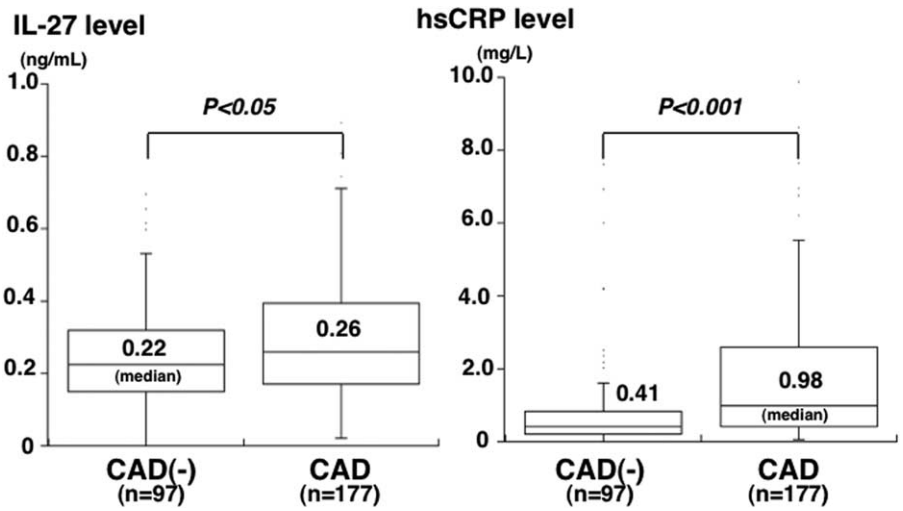

Figure 1. Plasma IL-27 and hsCRP levels of patients with and without CAD. Compared with 97 patients without CAD, 177 patients with CAD had higher IL-27 ($P<.05$ by the Mann–Whitney *U* test) and higher hsCRP ($P<.001$). The central line represents the median, the boxes span from the 25th to 75th percentiles, and the error bars extend from the 10th to 90th percentiles.

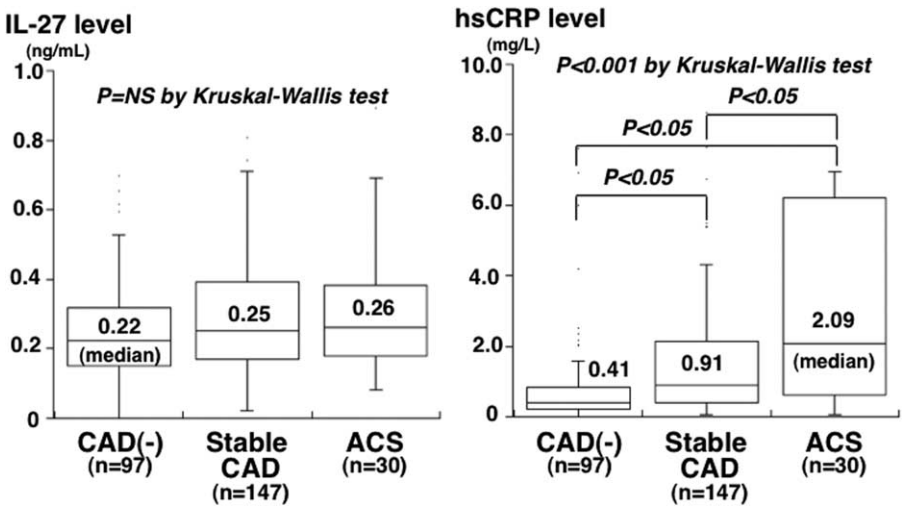

Figure 2. Plasma IL-27 and hsCRP levels in the 3 groups of CAD (-), stable CAD, and ACS. IL-27 levels did not differ among the 3 groups. However, hsCRP levels were significantly higher in ACS and stable CAD than in CAD (-) and were highest in ACS ($P < .001$ by the Kruskal–Wallis test).

hsCRP level (>1.0 mg/L). However, hsCRP levels were found to be the only independent factor for ACS, although IL-27 levels were not. The odds ratio for ACS was 3.84 (95% CI = 1.57–9.38, $P < .005$) for high hsCRP level.

4. Discussion

The present study reported plasma IL-27 levels to be high in patients with CAD and to be an independent factor associated with CAD. However, IL-27 levels did not differ significantly between ACS and stable CAD and only weakly correlated with the severity of CAD, defined as the numbers of stenotic coronary vessels and segments and the Gensini score. In contrast, hsCRP levels were highest in ACS and were an independent factor associated with both CAD and ACS. Moreover, hsCRP levels significantly correlated with the severity of CAD.

Regarding blood IL-27 levels in patients with CAD, Jafarzadeh et al[22] measured serum IL-27 levels in 60 patients with AMI, 60 with UAP, and 60 healthy controls with no risk factors. They reported IL-27 levels to be higher in patients with AMI and UAP than in controls, but there was no significant difference in IL-27 levels between AMI and UAP. Jin et al[11] investigated plasma IL-27 levels in 165 patients undergoing coronary angiography, of whom 136 had CAD (50 with AMI, 56 with UAP, and 30 with stable CAD) and 27 did not. They reported IL-27 levels to be higher in patients with stable CAD, UAP and AMI than in those without CAD and to be highest in patients with AMI. Unexpectedly, they showed that IL-27 levels correlated well

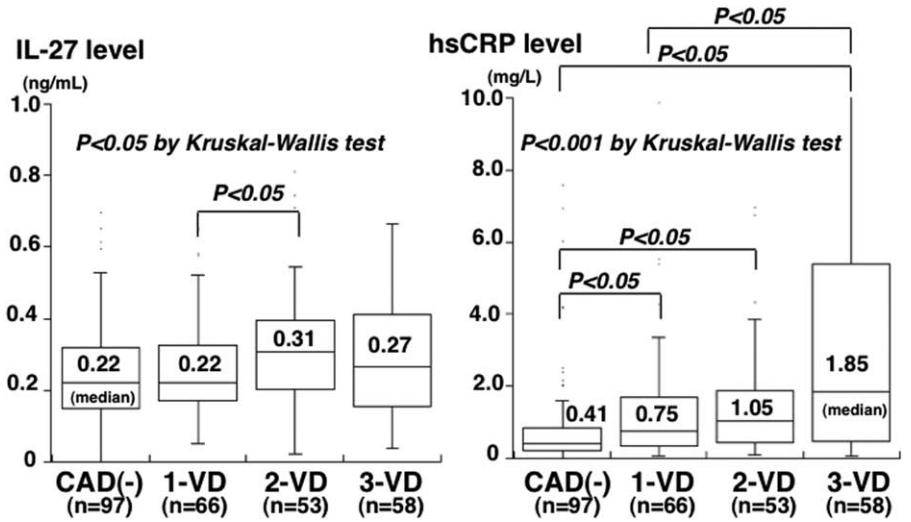

Figure 3. Plasma IL-27 and hsCRP levels and the number of stenotic coronary vessels. IL-27 levels tended to increase with the number of >50% stenotic vessels ($P < .05$ by the Kruskal–Wallis test). A stepwise increase in hsCRP levels was found ($P < .001$ by the Kruskal–Wallis test), and hsCRP levels were higher in 3-VD than in CAD (-) or 1-VD ($P < .05$ by the Steel–Dwass test). The central line represents the median, the boxes span from the 25th to 75th percentiles, and the error bars extend from the 10th to 90th percentiles. 1-VD = 1-vessel disease; 2-VD = 2-vessel disease; 3-VD = 3-vessel disease.

with the Gensini score (r = 0.84). In contrast, Lin et al[23] measured plasma IL-27 levels in 208 patients undergoing coronary angiography, of whom 161 had CAD (56 with AMI, 62 with UAP, and 43 with stable CAD). They reported IL-27 levels to be higher in patients with AMI and UAP, but not in stable CAD, than in those without CAD. No correlation between IL-27 levels and Gensini score was found. In the present study, we measured plasma IL-27 levels in 274 patients undergoing coronary angiography, of whom 177 had CAD (30 with NSTEMI or UAP and 147 with stable CAD) and 97 did not. We found IL-27 levels to be higher in patients with CAD than without CAD and to be an independent factor for CAD. However, there was no difference in IL-27 levels between ACS and stable CAD. IL-27 levels only weakly correlated with Gensini score and the number of stenotic coronary segment ($rs = 0.16$ and $rs = 0.15$). In contrast, hsCRP levels were highest in ACS and were an independent factor associated with both CAD and ACS. Moreover, hsCRP levels significantly correlated with Gensini score and the number of stenotic segments ($rs = 0.31$ and $rs = 0.35$). Thus, IL-27 levels in patients with CAD are high but are unlikely to be a good biomarker reflecting the severity of CAD or the presence of ACS. IL-27 may not play a major role in the progression of CAD.

IL-27 may regulate the immune responses with both pro- and ant-inflammatory properties,[5] and the major role of IL-27 in promoting or suppressing inflammation may vary among diseases.[11] In blood, high IL-27 levels were reported in patients with systemic sclerosis,[13] whereas low levels were reported in systemic lupus erythematosus.[29] Whether IL-27 accelerates or prohibits atherosclerosis remains unclear.[3] The present study and others[11,22,23] have shown blood IL-27 levels in patients with CAD to be high. IL-27 may play a promotive role in the development of CAD. However, IL-27 was reported to prohibit atherosclerosis in animal models,[20,21] suggesting its inhibitory role in atherosclerosis. Therefore, high IL-27 levels in patients with CAD may represent an adaptive mechanism aimed at preventing the progression of atherosclerosis. To clarify the role of blood IL-27 in the progression of CAD, further prospective studies with a large number of patients with CAD are needed.

Several limitations associated with the present study warrant mention. First, in the present study, angiography was used to evaluate coronary atherosclerosis. Coronary angiography cannot visualize plaques and only shows lumen characteristics, such as luminal diameter stenosis. Second, as we did not measure IL-27 levels in the coronary sinus, our study did not provide any information about the main sources of IL-27 in patients with CAD. Moreover, our study was cross-sectional in nature and could not establish causality, as it only depicted some associations and proposed some hypotheses. Third, the number of study patients was relatively small, especially patients with ACS. Our study included 274 patients undergoing elective coronary angiography [30 ACS, 147 stable CAD, and 97 CAD (-)]. However, the previous studies by Jin et al[11] and Lin et al[23] included only 165 [106 ACS, 30 stable CAD, and 27 CAD (-)) and 208 (118 ACS, 43 stable CAD, and 47 CAD (-)] patients undergoing coronary angiography, respectively. Our study had much more patients with stable CAD but fewer patients with ACS than the previous studies. In spite of the small number of patients with ACS, our study showed hsCRP, but not IL-27, levels to be significantly highest in ACS and to be an independent factor for ACS. Fourth, our study subjects were 177 patients with CAD and 97 without CAD. Because we did not have healthy controls and because some patients without CAD had mild, but not significant, stenosis, these may have confounded the results. Finally, our study was conducted in Japanese patients undergoing coronary angiography, who are generally considered as a highly select population at a high risk for CAD. Our results therefore may not be applicable to the general population or other ethnics.

5. Conclusion

While plasma IL-27 levels were high in patients with CAD, these levels were an independent factor for only CAD, not ACS, and weakly correlated with the severity of CAD. Our results suggest that IL-27 is unlikely to be a good biomarker reflecting the severity of CAD or the presence of ACS, or to play a major role in the progression of CAD.

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