

Original Article

Serum interleukin-6 and interferon-gamma are associated with the severity of coronary disease in patients with acute coronary syndrome and type-2 diabetes

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Abstract: A number of studies have suggested that interleukin 6 (IL-6) and interferon-gamma (IFN- γ) have pathophysiologic roles in cardiovascular diseases. In view of recent evidence that serum IL-6 and IFN- γ may serve as inflammatory mediators in patients with enhanced inflammation, we hypothesize both IL-6 and IFN- γ have diagnostic and prognostic value in patients with acute coronary syndrome (ACS) and type 2 diabetes (T2D). Patients with ACS and T2D (n=29), patients with ACS but without T2D (n=33), and patients with T2D but without ACS (n=42) were selected for the study. Thirty volunteers without ACS or T2D served as controls. Serum IL-6 and IFN- γ were measured, coronary angiography and echocardiography were performed, and Gensini scores were calculated. Higher serum IL-6 and IFN- γ levels existed in patients with ACS and T2D than patients with ACS or T2D alone ($P<0.05$); however, no significant differences existed between the T2D and control groups ($P>0.05$). Of the 29 ACS patients with T2D, the serum levels of IL-6 and IFN- γ in single-, double-, and triple-vessel lesion groups were higher than the control group ($P<0.05$), whereas the differences among the triple-vessel lesion groups were not significant. Gensini scores were positively correlated with serum IL-6 and IFN- γ in ACS patients. Based on stepwise regression analysis, increased serum IL-6 and IFN- γ were strong independent predictors of the Gensini score. These results indicate that elevated values of IL-6 and IFN- γ are associated with more intense inflammatory activity in patients with coronary instability. The inflammatory activity is even more intense in patients with T2D.

Keywords: Interleukin 6, interferon-gamma, coronary heart disease, severity

Introduction

Acute coronary syndrome (ACS) is often associated with coronary heart disease (CHD) through disruption of an atherosclerotic plaque, resulting in occlusion of the coronary artery [1] and increasing the potential development of ischemic heart disease and other cardiovascular diseases (CVDs) [2]. It has been recognized that diabetes is an independent risk factor for the atherosclerotic process which leads to ACS [3]. Studies have revealed that the incidence of CHD is 4 times higher in diabetic than non-diabetic women and 2.5 times higher in diabetic than non-diabetic men [4]. ACS patients with type 2 diabetes (T2D) are often misdiagnosed due to a lack of a clinical syndrome, resulting in delayed treatment.

Substantial evidence has revealed that ruptured coronary plaque trigger both a pro- and anti-inflammatory cytokine response [5]. Inflammatory cytokines, including IL-6 and IFN- γ , may be useful in predicting ACS and its prognosis. In addition, one of the well-characterized pathophysiologic states in patients with T2D, insulin resistance, is thought to be caused by chronic low-grade inflammation in adipose tissue, liver, and muscle [6].

Of note, the correlation between inflammatory cytokine levels in patients with ACS and T2D and the severity of coronary disease is unknown.

In this study we attempted to gain a greater conceptual insight into the relationship between inflammatory cytokines and severity of

IL-6 and IFN- γ in patients with ACS and diabetes

coronary artery disease in patients with ACS and T2D. Our hypothesis was that these cytokines may serve as effective biomarkers in predicting disease severity and prognosis in such patients.

Patients and methods

Ethics statement

All of the protocols used for the current research were approved by the Human Rights Committee at the Second Hospital of Shandong University, and all subjects gave written informed consent before participation.

Study population

Between August 2013 and February 2014, 104 patients (62 males; mean age, 58.50 ± 12.54 y; age range, 40-78 y) were recruited from the Department of Cardiology in the Second Hospital of Shandong University. All of the ACS patients had coronary artery disease confirmed by coronary angiography. The patients were classified into the following three groups: patients with ACS and T2D; patients with ACS but without T2D; and patients with T2D but without ACS. Thirty healthy subjects (17 males; mean age, 51.50 ± 12.81 y; age range, 42-76 y) were also recruited for the study who had no signs of ischemic heart disease, ECG criteria suggestive of ACS, abnormal glucose tolerance, and/or a history of cardiovascular disease or diabetes.

Nineteen patients with ACS had ST elevation acute myocardial infarction (STEMI) and 43 had unstable angina pectoris (UAP). STEMI was defined as prolonged chest pain accompanied by ischemic ST-T elevation and was confirmed by elevation of the plasma creatine kinase-MB (CK-MB) level greater than twice the upper limit of normal, and a troponin-I level >0.5 ng/ml [7]. UAP was defined as chest pain at rest with ST segment depression of at least 0.1 mV or T-wave inversion in two or more continuous electrocardiographic leads and no elevation of CK-MB or troponin-I [8]. Patients with T2D were defined according to the updated global guideline [9] and/or prior use of an anti-diabetic medication.

The exclusion criteria for this study included pregnancy, previous myocardial infarction, a

history of heart failure, myocardopathy or moderate-to-severe valvular heart disease, prior stroke, arterial or venous thromboembolic disease, peripheral artery disease, impaired renal function (glomerular filtrate rate by MDRD-4 <60 mL/min/1.73 m²), hepatic dysfunction (ALT >2.5 times the upper limit of reference), active or recent infection (last month), a history of an inflammatory or connective tissue disorder, chronic or occasional (last 3 weeks) anti-inflammatory or corticosteroid treatment, cancer, a hematologic disorders, and previous major trauma or surgery (within 3 months).

Clinical and laboratory assessment

Detailed baseline questionnaires were collected at study entry, including age, gender, medical history, smoking history, and medication. Blood glucose levels were measured immediately before the procedure before intravenous fluids were administered. The Tnl and CK-MB samples were collected before the procedure. The total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and glycated hemoglobin (HbA1C) levels were determined using standard laboratory methods, and all assays were conducted in the main clinical laboratories of the Second Hospital of Shandong University.

Peripheral blood samples were obtained within 48 h of hospital admission prior to coronary angiography in all cases, and usually the morning following admission with the patient fasting overnight. All serum samples were stored at -80°C for subsequent analyses. Serum levels of IL-6 and IFN- γ were determined using a commercially available enzyme-linked immunosorbent assay kit (Quantikine; R&D Systems, Minneapolis, MN, USA) according to the manufacturer's protocol. Measurements were performed in duplicate and the results were averaged. The sensitivity of the IFN- γ ELISA kit was 15 pg/ml and the standard curve range was 15-2000 pg/ml. The sensitivity of the IL-6 ELISA kit was 4 pg/ml and the standard curve range was 4-500 pg/ml.

Coronary angiography and echocardiography

Coronary angiography was performed by left-heart catheterization and arteriography using the Judkins method [10]. The Gensini score was calculated to determine the severity of coronary atherosclerosis. The left ventricular end-

IL-6 and IFN- γ in patients with ACS and diabetes

Table 1. Comparison of baseline demographic and clinical characteristics of the four groups

Clinical variables	ACS-T2D group	ACS group	T2D group	Control group	P value
No. of patients	29	33	42	30	
Age (years)	61.9 \pm 12.7	58.4 \pm 7.5	56.2 \pm 8.4	60.5 \pm 12.8	0.259
Male (%)	15 (51.72%)	19 (57.58%)	28 (66.67%)	17 (56.67%)	0.527
Medical history					
Hyperlipidemia (%)	10 (34.48%) [#]	20 (60.61%) ^Δ	16 (38.10%)	0	0.011
Hypertension (%)	8 (27.59%) [#]	19 (57.58%) ^{Δ, *}	13 (30.95%) [*]	0	0.040
Family History of CHD (%)	3 (10.34%)	4 (12.12%)	0	0	0.670
Smoking history (%)	7 (24.14%) [*]	10 (30.30%) [*]	8 (18.63%) [*]	3 (7.50%)	0.041
Medication					
Nitrates (%)	19 (65.52%)	17 (51.52%)	0	0	0.39
Diuretic (%)	10 (34.48%)	14 (42.42%)	0	0	0.41
Beta blocker (%)	22 (75.86%)	21 (63.64%)	0	0	0.08
ACEI (%)	8 (27.59%)	11 (33.33%)	0	0	0.21
Calcium antagonist (%)	19 (65.52%)	18 (54.55%)	0	0	0.26
Statin (%)	20 (68.97%)	24 (72.73%)	0	0	0.14
Clinical characteristics					
Heart rate (beat/min)	78.76 \pm 8.04	75.93 \pm 5.36	70.07 \pm 9.50	73.71 \pm 10.14	0.127
SBP (mmHg)	139.21 \pm 13.62	134.34 \pm 11.13	118.14 \pm 7.74	119.14 \pm 12.62	0.288
DBP (mmHg)	85.01 \pm 9.48	84.31 \pm 3.57	81.92 \pm 2.49	80.00 \pm 4.06	0.148
LVEDV (ml)	118.90 \pm 25.26	107.58 \pm 12.17	96.72 \pm 17.79	106.70 \pm 16.61	0.510
LVESV (ml)	52.60 \pm 24.28	45.42 \pm 9.34	33.55 \pm 11.50	40.04 \pm 9.82	0.599
LVEF (%)	48.00 \pm 6.77	51.30 \pm 7.06	61.00 \pm 3.96	64.20 \pm 6.08	0.124

Age and clinical characteristics are expressed as the mean \pm SD. Other data are expressed as number of individuals (percentage). Abbreviations: ACS: Acute coronary syndrome; T2M: Type 2 diabetes; CHD: Coronary heart disease; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LVEDV: Left ventricular end-diastolic volume; LVESV: Left ventricular end-systolic volume; LVEF: Left ventricular ejection fraction. Compared with ACS group, [#] P <0.05, ^{##} P <0.01; compared with T2D group, ^Δ P <0.05, ^{ΔΔ} P <0.01; compared with control group, ^{*} P <0.05, ^{**} P <0.01.

systolic volume (LVESV) and the left ventricular end-diastolic volume (LVEDV) were measured using Simpson's method (Vivid-7; GE Medical System, [city, state, country?]), and the left ventricular ejection fraction (LVEF) was calculated as follows: $LVEF = (LVEDV - LVESV) / LVEDV \times 100\%$.

Statistical analysis

All data analyses were performed using SPSS for Windows (version 17.0; SPSS, Inc., Chicago, IL, USA). Data are presented as proportions, mean \pm SD, geometric mean (SD range), or in the case of variables which did not conform to a normal or log-normal distribution, the median [inter-quartile range {IQR}]. For independent samples, two-way comparisons for proportions were analyzed using Fisher's exact test, normally distributed variables were analyzed using Student's t-test, and non-normally distributed variables were analyzed using the

Mann-Whitney U-test. For correlation analyses, Person's correlation was used for normally distributed variables and Spearman's correlation was used for non-normally distributed variables. Predictors associated with the Gensin score were determined by stepwise linear regression analysis. P values <0.05 were considered statistically significant.

Results

Baseline patient characteristics

The baseline characteristics of the four groups are shown in **Table 1**. There were no significant differences in age, gender, heart rate, LVEDV, LVESV, and LVEF among the four groups. A greater number of patients in the ACS group had a history of hyperlipidemia and hypertension than the patients in the ACS-T2D and T2D groups. A greater number of patients in the

IL-6 and IFN- γ in patients with ACS and diabetes

Table 2. Comparison of serum levels of IL-6 and IFN- γ and other laboratory data of the four groups

	ACS-T2D group	ACS group	T2D group	Control group	P value
No. of patients	29	33	42	30	
IL-6 (pg/ml)	15.68 \pm 4.84 ^{**Δ}	12.46 \pm 2.97 ^{**Δ}	6.58 \pm 1.21	3.24 \pm 0.17	<0.01
IFN- γ (pg/ml)	2.80 \pm 0.51 ^{**Δ}	1.92 \pm 0.31 ^{**Δ}	0.51 \pm 0.06	0.16 \pm 0.02	<0.01
HbA1c (%)	6.7 \pm 1.45	5.1 \pm 2.02 ^{Δ}	7.68 \pm 0.93 [*]	5.7 \pm 1.0	0.027
hs-CRP (mg/L)	5.47 \pm 1.46 ^{#Δ*}	2.32 \pm 1.59	1.01 \pm 0.43	0.92 \pm 0.44	0.048
NT-proBNP (pg/ml)	657.14 \pm 107.1 ^{Δ*}	550.08 \pm 110.78 ^{Δ*}	115.43 \pm 28.17	160.96 \pm 58.11	0.035
HDL-C (mmol/L)	0.82 \pm 0.21	0.99 \pm 0.18	1.03 \pm 0.22	1.16 \pm 0.27	0.106
LDL-C (mmol/L)	4.46 \pm 1.13 ^{#Δ*}	2.76 \pm 1.09	2.17 \pm 0.68	1.97 \pm 0.57	0.038
TC (mmol/L)	5.41 \pm 2.36	4.65 \pm 1.27	3.54 \pm 0.79	3.45 \pm 0.18	0.446
TG (mmol/L)	1.87 \pm 0.94	1.17 \pm 0.74	2.04 \pm 0.89	1.46 \pm 0.75	0.312
Gensini score	32.7 \pm 23.0	16.3 \pm 8.6	0	0	0.187
Single-vessel lesion (n; %)	9 (31.03%)	14 (42.42%)			0.137
Double-vessel lesion (n; %)	7 (24.14%)	5 (15.15%)			0.245
Triple-vessel lesion (n; %)	13 (44.83%)	7 (21.21%)			0.101

Abbreviations: IL-6: Interleukin-6; IFN- γ : Interferon-gamma; HbA1c, Glycated hemoglobin A1c; hs-CRP: High-sensitivity C-reactive protein; NT-proBNP: N-terminal pro-brain natriuretic peptide; HDL-C: High-density lipoprotein; LDL-C: Low-density lipoprotein; TC: Total cholesterol; TG: Triglycerides. Compared with ACS group, # P <0.05, ## P <0.01; compared with T2D group, Δ P <0.05, $\Delta\Delta$ P <0.01; compared with control group, * P <0.05, ** P <0.01.

Table 3. Comparisons of serum IL-6 and IFN- γ in single-, double-, and triple-vessel disease in ACS patients with T2D

Groups	n	IL-6 (pg/ml)	IFN- γ (pg/ml)
Single-vessel lesion group	9	13.96 \pm 5.31 ^{**}	2.20 \pm 0.10 ^{**}
Double-vessel lesion group	7	14.93 \pm 3.01 ^{**}	2.69 \pm 0.16 ^{**}
Triple-vessel lesion group	13	17.27 \pm 5.10 ^{**}	3.27 \pm 0.27 ^{**}
Control group	30	3.24 \pm 0.17	0.16 \pm 0.02
		F=10.21	χ^2 =15.80
		P=0.02	P<0.01

Compared with control group, ** P <0.01.

Comparison of serum levels of IL-6 and IFN- γ among the groups with different lesions and ACS patients with T2D

In patients with ACS and T2D, the serum levels of IL-6 and IFN- γ in the single-, double-, and triple-vessel lesion groups were higher than that in control group (P <0.01), and the differences among the three groups were not significant (P >0.05; **Table 3**).

ACS-T2D, ACS, and T2D groups had a smoking history than the control group. No significant difference existed in prescribed medication use between the ACS-T2D and ACS groups. The ACS group had a higher SBP and DBP than the other three groups, but the difference was not significant.

Comparison of serum levels of IL-6 and IFN- γ among the four groups

Higher serum levels of IL-6, IFN- γ , hs-CRP, and NT-proBNP existed in the ACS-T2D group than patients in the ACS or T2D groups (P <0.05). Higher serum levels of LDL-C existed in the ACS group than the ACS-T2D or T2D group. In contrast, serum levels of IL-6 and IFN- γ in the T2D group did not differ significantly from the control group (P >0.05; **Table 2**).

Relationship between the Gensini score and serum IL-6, serum IFN- γ , HbA1C, hs-CRP, and NT-proBNP in ACS patients

To assess the predictive markers associated with the severity of coronary disease, the levels of serum IL-6, serum IFN- γ , HbA1C, hs-CRP, and NT-proBNP were analyzed as a function of the Gensini scores. Bivariate correlation analysis showed a significant positive correlation with serum IL-6, serum IFN- γ , HbA1C, hs-CRP, and NT-proBNP in ACS patients (R =0.726, 0.562, 0.429, 0.546, and 0.487, respectively; P ≤0.001; **Table 4**). The serum IL-6 and serum IFN- γ levels were positively correlated with the Gensini scores in patients with ACS and T2D (R =0.860 and 0.719, respectively; P <0.001); however, the HbA1C and NT-proBNP levels had no apparent correlation with the Gensini score.

IL-6 and IFN- γ in patients with ACS and diabetes

Table 4. Correlation between the severity of coronary disease and cardiovascular risk factors in ACS patients

	Entire ACS		ACS-T2 group		ACS group	
	R	P	R	P	R	P
Gensini score						
IL-6	0.726	<0.001	0.860	<0.001	0.466	0.006
IFN- γ	0.562	<0.001	0.719	<0.001	0.311	0.079
HbA1c	0.429	0.001	0.263	0.168	0.30	0.09
hs-CRP	0.546	<0.001	0.40	0.032	0.502	0.003
NT-proBNP	0.487	<0.001	0.275	0.148	0.364	0.037

Table 5. Stepwise linear regression analysis for Gensini score estimation in ACS patients

	Entire ACS		ACS-T2D group		ACS group	
	β	P	β	P	β	P
IL-6	0.534	<0.001	0.546	<0.001	0.466	0.006
IFN- γ	0.372	0.001	0.412	0.004		

resin patients with ACS and T2D ($P>0.05$). Furthermore, stepwise linear regression analysis revealed that the serum IL-6 and IFN- γ levels were powerful predictors of the severity of coronary disease in patients with ACS and T2D (Table 5).

Discussion

In the present study, elevated IL-6 and IFN- γ levels were demonstrated in patients with ACS and T2D compared to patients with ACS or T2D alone, which is consistent with our hypothesis. The observed significant increase in the level of pro-inflammatory factors indicated an enhanced inflammatory state in patients with ACS and T2D and showed that hyperglycemia is correlated with increased inflammatory cytokine expression, which may play a role in the development of coronary heart disease in patients with T2D. Coronary plaque rupture triggers an inflammatory cascade [11] and an enhanced inflammatory state is linked to plaque instability. In addition, impaired glucose signaling in patients with T2D causes hyperglycemia, which stimulates insulin secretion and sustained physiologic hyperinsulinemia activates multiple genes involved in inflammation [12], thus resulting in a robust release of various pro-inflammatory cytokines. These cytokines can also lead to an alteration in insulin sensitivity and disruption of glucose homeostasis, which is an atherosclerotic risk factor and

leads to coronary artery disease [13].

T2D confers an increased risk for developing coronary heart disease and recurrent ischemic events after ACS [14], and predicts future adverse coronary vascular events as well as early death [15]. Painless ACS is frequently observed in patients with diabetes, thus resulting in a delay of diagnosis and treatment in such patients. Rather than coronary intervention, early diagnosis and proper preventive therapy are more crucial for reducing the mortality of such high-risk patients [16].

Inflammatory responses play a crucial role in ACS progression, and pro-inflammatory cytokines have been shown to be useful for predicting ACS and its prognosis [17]. In addition, T2D is considered an inflammatory process with systemic involvement of the vascular tree [18]. Both IL-6 and IFN- γ have been shown to improve the baseline clinical prognostication of ACS patients, but less is known about the relationship between these biomarkers and the severity of coronary disease in patients with ACS and T2D. Therefore, we sought to elucidate this relationship and attempted to determine the potential diagnostic and prognostic role of IL-6 and IFN- γ in patients with ACS and T2D.

IL-6 is a Th17-related cytokine which exerts potent pro-inflammatory effects [19], and can promote coronary plaque instability. In addition to plaque rupture, myocardial stretch may also stimulate IL-6 expression [20]. Studies have demonstrated that patients with myocardial infarctions, the IL6 level is significantly higher in the acute phase of the myocardial infarction compared to the control group [21]. Furthermore, the elevated serum IL-6 level has been linked with the development of coronary artery disease [22]. In the current study, patients with ACS and T2D were shown to have higher levels of IL-6, suggesting an exaggerated inflammatory response, which might be of importance in establishing the diagnosis and prognosis of such patients. IFN- γ is the signature cytokine of Th1 cells and the main activator of macro-

phages and endothelial cells. By stimulating the expression of adhesion molecules on the surface of endothelial cells and decreasing the synthesis of collagen [23], IFN- γ can destabilize the plaque. As an important cytokine involved in clinical inflammation, IFN- γ was probed as an inflammatory biomarker of plaque vulnerability and might serve as a novel biomarker for evaluating disease severity and predicting clinical outcome in patients with ACS and T2D.

This study also showed, for the first time, an association between increased serum levels of IL-6 and IFN- γ and severity of coronary disease in ACS patients with different lesions. In addition, correlation and regression analyses showed that increased serum levels of IL-6 and IFN- γ were positively correlated with Gensini scores in ACS patients, which indicated that increased serum IL-6 and IFN- γ were involved in the severity of patients with ACS and T2D. The relationship between levels of pro-inflammatory cytokines and severity of coronary disease in the early stages of CHD supports the argument that acute ischemia causes activation of the inflammatory process, and the subsequent increased synthesis of proinflammatory factors and systemic inflammation in T2D might intensify the underlying process.

Conclusions

This is the first study to analyze the diagnostic value of IL-6 and IFN- γ in patients with ACS and T2D. We conclude that elevated levels of IL-6 and IFN- γ are associated with more severe coronary disease in patients with ACS and T2D. We tentatively conclude that abnormally pro-inflammatory cytokine levels in ACS patients might be associated with plaque instability and hyperglycemia might accelerate the process. Thus, these biomarkers might represent a useful and cost-effective means of identifying the subset of patients with ACS and T2D who require special attention to establish a diagnosis and initiate treatment in a timely fashion.

Limitations

This study had some limitations, such as the relatively small sample size, which might be a reason for some of the results that demonstrated no statistical significance. Indeed, statistical significance might be increased with a larger number of patients. In addition, this was

a cross-sectional observational study conducted in a single center. Multicenter prospective cohort studies and serial evaluation of these cytokines over a longer duration of time are essential to determine the clinical application of these cytokines.

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Disclosure of conflict of interest

None.

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IL-6 and IFN- γ in patients with ACS and diabetes

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