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Interleukin-6 as an Independent Predictor of Future Cardiovascular Events in Patients with Type-2 Diabetes without Structural Heart Disease

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Abstract

Background: An increased serum interleukin-6 (IL-6) level is associated with a risk of cardiovascular disease. Elevated IL-6 levels are also involved in the pathogenesis of insulin resistance and can predict the development of type-2 diabetes. We tested the hypothesis that elevated IL-6 levels can predict the incidence of cardiovascular events in type-2 diabetes.

Methods: Eighty-two patients with type-2 diabetes without structural heart disease (48 males; 60 ± 12 years). The initial onset of a major adverse cardiovascular event was investigated.

Results: During a mean of 3.4 ± 2.0 years of follow-up, 11 patients developed cardiovascular events (3 cardiovascular deaths, 2 non-fatal myocardial infarctions, 2 coronary revascularizations, and 4 strokes). Univariate analyses revealed that elevated IL-6 level, fasting immunoreactive insulin level, and the HOMA-R were associated with cardiovascular events. Based on multivariate analyses, elevated IL-6 levels independently predicted the incidence of cardiovascular events (HR 1.17, 95% CI 1.04–1.31, P=0.015). Kaplan–Meier curves revealed that patients with a high IL-6 concentration (>2.6 pg/mL) had a higher incidence of cardiovascular events than those with non-high IL-6 concentration (≤2.6 pg/mL, P=0.031).

Conclusions: These results suggest that measurement of serum IL-6 concentration is a useful tool to identify high-risk patients for cardiovascular events in type-2 diabetes.

Keywords: Cardiovascular event; Diabetes mellitus; Interleukin-6

Abbreviations: BMI: Body Mass Index; BP: Blood Pressure; CHD: Coronary Heart Disease; CVD: Cardiovascular Disease; ECG: Electrocardiography; HbA1c: Hemoglobin A1c; HDL: High-Density Lipoprotein; HOMA-R: Homeostasis Model Assessment Ratio; IL-6: Interleukin-6; ^{123}I-MIBG: Iodine-123 metaiodobenzylguanidine; IRI: Immunoreactive Insulin; LDL: Low-Density Lipoprotein; MACCE: Major Adverse Cardiac and Cerebrovascular Event; MI: Myocardial Infarction; T2DM: Type-2 Diabetes

Introduction

Inflammatory processes are major contributors to cardiovascular disease [1]. Interleukin-6 (IL-6) is known to be an inflammatory marker [2]. An increased serum level of IL-6 is associated with an increased risk of cardiovascular disease [3,4]. Elevated levels of IL-6 are also involved in the pathogenesis of insulin resistance, and can be used to predict the development of type-2 diabetes (T2DM) [5-7]. T2DM is a pro-inflammatory condition [8], and increases the risk of coronary heart disease (CHD). It has been suggested serum IL-6 levels may be a biochemical marker estimating the risk of cardiovascular disease (CVD). However, the relationship between serum IL-6 levels and risk of CVD in T2DM patients without organic heart disease has not been adequately investigated.

We tested the hypothesis that elevated IL-6 levels could predict the incidence of cardiovascular events in patients with T2DM without organic heart disease.

Methods

This investigation was conducted according to the principles expressed in the Declaration of Helsinki. All subjects gave their written informed consent to participate in the study. The study protocol was approved by the Ethics Committee of Oita University Hospital (Oita, Japan).

Study population

Eighty-five patients with T2DM admitted to Oita University Hospital from 2002 to 2004 for control of blood glucose levels were recruited. Patients were excluded if they were ≥80 years old. T2DM was defined as a fasting plasma glucose concentration >126 mg/dL, a 2-h plasma glucose concentration following a 75-g oral glucose load of ≥200 mg/dL, or self-reported use of anti-diabetic medication [9]. None of the patients had organic heart disease as determined by physical examination, chest radiography, 12-lead electrocardiography (ECG), echocardiography, and cardiac ^{201}thallium scintigraphy. Myocardial ischemia was excluded by treadmill-exercise ECG testing. All patients had clinical examinations to exclude secondary hypertension. Essential hypertension was defined as diastolic blood pressure (BP) ≥90 mmHg, systolic BP ≥140 mmHg or self-reported use of anti-hypertensive medication [10]. Dyslipidemia was defined as fasting triglycerides ≥150 mg/dL, low-density lipoprotein (LDL)-cholesterol ≥140 mg/dL and high-density lipoprotein (HDL)-cholesterol <40 mg/dL [11].

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Laboratory methods

Blood was taken after an overnight fast at 7 am from the antecubital vein with the patient in the recumbent position. All patients had routine laboratory tests, including assays for serum electrolytes, serum total cholesterol, serum triglycerides, serum HDL and LDL cholesterols, fasting plasma glucose, and fasting immunoreactive insulin (IRI). Insulin resistance was evaluated using the homeostasis model assessment ratio (HOMA-R):

[Fasting IRI (μU/mL) × fasting plasma glucose (mmol/L)]/22.5.

Serum total IL-6 levels were determined using a Human IL-6 CLEA kit (Fujirebio, Tokyo, Japan). All patients were stratified into two groups based on median serum IL-6 level. The high IL-6 group was defined as >2.6 pg/mL. Thirty patients in the high IL-6 group and 22 patients in the non-high IL-6 group met the criteria for essential hypertension, respectively; 43 of the 52 patients were being treated with Ca channel antagonist, β blocker, angiotensin-converting enzyme inhibitor, and/or angiotensin II receptor blocker, and 9 patients were being treated with diet therapy alone. None of the patients was being treated with α blocker. Urinary excretion was measured using urine samples collected over 24 h. The body mass index (BMI) was calculated as weight/height^2 (kg/m^2).

Follow-up

Most of the follow-up of patients occurred at Oita University Hospital. Information was obtained from those patients whose follow-up was undertaken by a general practitioner. Information on the patients who were hospitalized in other departments was also obtained. For the patients who died, the cause of death was documented with the help of the patients' family and general practitioner.

The study endpoint was defined as the appearance of a major adverse cardiac and cerebrovascular event (MACCE), which included cardiovascular mortality, non-fatal myocardial infarction (MI), coronary revascularization through angioplasty or bypass and stroke. Using this combined criterion, only the first event was taken into account in the statistical analysis. Of the 85 patients enrolled, we obtained accurate follow-up information for 82 patients (49 males; mean age, 60 ± 12 years) for 3.4 ± 2.0 years. During follow-up, 3 patients died (4%): two were cardiovascular deaths and one was attributed to non-cardiovascular causes.

Statistical analyses

Data are mean ± SD. The chi-square test was used for categorical variables, and the analysis of variance (ANOVA) test was used for continuous variables. Differences between groups were analyzed using unpaired Student's test. Kaplan–Meier MACCE-free analyses were used to compare MACCE-free times between high and non-high IL-6 groups. To test for differences between the resulting curves, the log-rank test was used. Univariate and multivariate Cox proportional hazards regression analyses were undertaken to identify independent predictors (risk factors) of MACCE. Risk factors entered into the risk model included age, hypertension, dyslipidemia, the BMI, systolic and diastolic blood pressures, duration of T2DM, serum IL-6, fasting plasma glucose, fasting IRI, hemoglobin A1c (HbA1c), the HOMA-R, serum triglycerides, serum HDL and LDL cholesterols, serum uric acid and creatinine clearance. Results are given as hazard ratios (HRs) with 95% confidence intervals (CIs). P<0.05 was considered significant. All computations were done with JMP version 9.0.0 (SAS, Cary, NC, USA) running under a Windows 7 operating system (Microsoft, Redmond, WA, USA).

Results

Patient characteristics

Baseline patient characteristics of the non-high and high IL-6 groups are presented in Table 1. The mean ages of the groups were similar. There were no significant differences between the groups with respect to sex, number of current smokers, patients with hypertension or dyslipidemia, and in the use of any drugs. The BMI was higher in the high IL-6 group than in the non-high IL-6 group (P=0.015). The duration of T2DM was longer in the high IL-6 group than in the non-high IL-6 group (P=0.036). However, there were no significant differences in the levels of fasting plasma glucose, fasting IRI and HbA1c as well as the HOMA-R. Serum levels of triglyceride, HDL and LDL cholesterols and uric acid were not significantly different between the two groups. The creatinine clearance rate was not significantly different between the two groups.

Univariate and multivariate predictors of MACCE

During follow-up, 11 patients presented with a MACCE (13%). Of these, 3 were cardiovascular deaths, 2 were non-fatal MI, 2 were coronary revascularizations, and 4 were strokes (Table 2). MACCEs occurred more frequently in the high IL-6 group (22%) than in the non-high IL-6 group (5%, P=0.023). Results of univariate and multivariate Cox proportional hazards regression analyses of MACCE are presented in Table 3 and 4, respectively. Univariate analyses revealed that serum IL-6 level, fasting IRI level and the HOMA-R were associated with

	Non-high IL-6 group (≤2.6 pg/mL) (n=41)	High IL-6 group (>2.6 pg/mL) (n=41)	*P*
Female/male	14 / 27	19 / 22	0.368
Age (years)	59 ± 12	61 ± 12	0.566
Current smoker (%)	58.5	43.9	0.269
Hypertension (%)	53.6	73.2	0.108
Dyslipidemia (%)	73.2	87.8	0.162
Drug use (%)			
Statin	36.6	48.8	0.372
Ca channel antagonist	34.1	48.8	0.262
ACE inhibitor / ARB	26.8	39.0	0.347
α blocker	7.3	0	0.241
BMI (kg/m^2)	23.9 ± 5.3	26.8 ± 5.4	0.015*
Systolic BP (mmHg)	129 ± 23	130 ± 21	0.956
Diastolic BP (mmHg)	71 ± 14	68 ± 14	0.298
Duration of diabetes (years)	7.95 ± 7.27	11.95 ± 9.53	0.036*
Fasting plasma glucose (mg/dL)	156 ± 49	146 ± 41	0.318
Fasting IRI (μU/mL)	8.33 ± 5.36	11.32 ± 7.63	0.437
HOMA-R	3.13 ± 2.23	4.04 ± 2.87	0.115
HbA1c (%)	8.89 ± 1.89	8.18 ± 1.42	0.057
Triglycerides (mg/dL)	136 ± 83	185 ± 216	0.180
HDL cholesterol (mg/dL)	45.9 ± 13.2	45.9 ± 15.3	0.985
LDL cholesterol (mg/dL)	117 ± 28	123 ± 40	0.460
Uric acid (mg/dL)	5.24 ± 1.64	5.84 ± 1.68	0.104
Creatinine clearance (mL/min)	114.3 ± 43.0	97.1 ± 43.5	0.076
IL-6 (pg/mL)	1.59 ± 0.55	6.33 ± 4.60	<0.001**

Data are mean ± SD. ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; HOMA-R, homeostasis model assessment ratio; IL-6, interleukin-6; IRI, immunoreactive insulin; LDL, low-density lipoprotein. *p<0.05, **p<0.01

Table 1: Clinical Characteristics of the Study Patients.

MACCE (Table 3). In the multivariate analysis using risk factors including serum IL-6 level, fasting IRI level and the HOMA-R, only serum IL-6 level independently predicted the incidence of MACCE (HR, 1.17, 95% CI, 1.04–1.31, P=0.015, Table 4).

Kaplan–Meier MACCE-free estimation

The MACCE-free ratio as evaluated by Kaplan–Meier analyses was significantly lower in the high IL-6 group than in the non-high IL-6 group (P=0.031, Figure 1).

Discussion

In the present study, 82 T2DM patients were followed up for a mean period of 3.4 ± 2.0 years, and MACCE occurred in 13 of them. The most important finding was that a high IL-6 concentration can accurately predict cardiovascular events in T2DM patients without structural heart disease. This is the first report to demonstrate the long-term predictive value of serum IL-6 concentration of CVD in these patients. The MACCE-free ratio as evaluated by Kaplan–Meier analyses was significantly lower in the high IL-6 group than in the non-high IL-6 group.

Increased serum IL-6 levels are associated with CHD, stroke and cardiovascular mortality [12]. It has been reported that, during long-term follow-up, increased IL-6 levels are strongly associated with future cardiac events and mortality in a population with stable CHD [13]. Maeda et al. [14] reported that a high IL-6 level after optimized treatment for heart failure was an independent risk factor for morbidity and mortality in patients with congestive heart failure. It was recently reported that serum IL-6 level was significantly correlated with incident primary cardiovascular events in DM patients, the same as in non-diabetic populations [15]. IL-6 is one of the candidates responsible for adipose tissue-related insulin resistance. Serum IL-6 level has been reported to be high in patients with obesity or T2DM [16,17]. The present study demonstrated that elevated IL-6 levels were involved in the incidence of cardiovascular events in patients with T2DM. The precise mechanisms underlying the interactions between high IL-6 levels and the incidence of cardiovascular events remain unclear. However, there are several mechanisms that could explain the relationship between these phenomena. Firstly, IL-6 is produced mainly by leukocytes, but partly also by cardiomyocytes and vascular endothelial cells [18,19]. It has been reported that ischemic and hypoxic conditions stimulate IL-6 production [20,21]. Those reports suggest that elevated IL-6 levels at baseline might be induced by silent cerebral or myocardial ischemia. Secondly, IL-6 is a pleiotropic cytokine with a broad range of humoral and cellular immune effects related to inflammation [2]. Elevated IL-6 levels can contribute to the development and instability of atherosclerotic plaques by activation of leukocytes and endothelial cells or by the induction of various cytokines. Therefore, serum IL-6 levels might reflect the progression of vascular lesions. Thirdly, impaired autonomic neural activity has been recognized as a crucial risk factor for cardiac dysfunction, and is strongly associated with an increased risk for harmful events and overall mortality in DM patients [22-24]. Cardiac iodine-123 metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy is a sensitive method for detecting cardiac sympathetic dysfunction [25,26]. We recently demonstrated that the abnormal washout rate of cardiac ^{123}I-MIBG scintigraphy at baseline was involved in the incidence of cardiovascular events in T2DM patients without structural heart disease [27]. In addition, using cardiac MIBG imaging, we reported that elevated IL-6 levels are associated with depressed cardiovascular autonomic function in T2DM patients [28]. Thus, we suggest that elevated IL-6 levels might cause cardiovascular events through cardiovascular autonomic dysfunction.

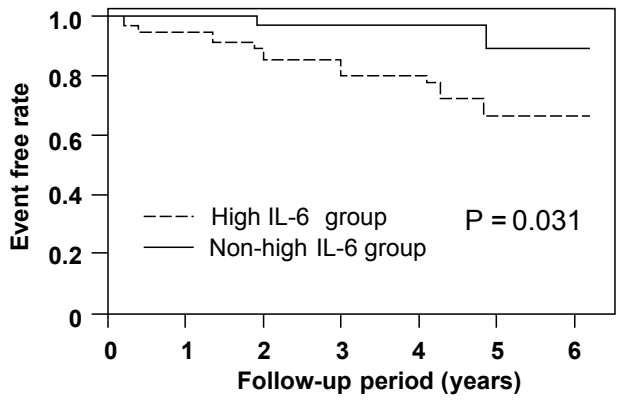

Figure 1: Kaplan–Meier event-free curves for major adverse cardiac and cerebrovascular events (MACCE) in the two groups. The black line and red line indicate non-high IL-6 group (≤2.6 pg/mL) and high IL-6 group (>2.6 pg/mL), respectively.

	Non-high IL-6 group (≤2.6 pg/mL)	High IL-6 group (>2.6 pg/mL)
Cardiovascular death	1	2
Non-fatal MI	1	1
Coronary revascularization	0	2
Stroke	0	4
Total	2	9

MI, myocardial infarction. Other abbreviations are as shown in Table 1

Table 2: Number of Patients Achieving the Study Endpoints.

	Hazard ratio (95% CI)	P
Age (10 years)	1.60 (0.90–3.07)	0.111
Hypertension (yes)	2.16 (0.56–14.20)	0.287
Dyslipidemia (yes)	2.84 (0.54–52.07)	0.253
BMI (1 kg/m^2)	1.10 (0.99–1.20)	0.075
Systolic BP (10 mmHg)	1.23 (0.93–1.65)	0.152
Diastolic BP (10 mmHg)	1.06 (0.67–1.73)	0.805
Duration of diabetes (years)	1.02 (0.95–1.08)	0.574
IL-6 (1 pg/mL)	1.18 (1.05–1.30)	0.008*
Fasting plasma glucose (10 mg/dL)	1.01 (0.89–1.14)	0.834
Fasting IRI (μU/mL)	1.11 (1.03–1.19)	0.006*
HOMA-R	1.21 (1.03–1.38)	0.019*
HbA1c (1%)	0.94 (0.63–1.33)	0.735
Triglycerides (10 mg/dL)	1.02 (0.99–1.04)	0.087
HDL cholesterol (5 mg/dL)	1.14 (0.93–1.37)	0.205
LDL cholesterol (10 mg/dL)	0.96 (0.81–1.12)	0.633
Uric acid (mg/dL)	1.21 (0.86–1.69)	0.248
Creatinine clearance (10 mL/min)	0.92 (0.77–1.08)	0.311

Abbreviations are as shown in Table 1. *p<0.05.

Table 3: Predictors of future MACCEs by univariate Cox regression analyses.

	Hazard ratio (95% CI)	P
IL-6 (1 pg/mL)	1.17 (1.04–1.31)	0.015*
Fasting IRI (1 pg/mL)	1.11 (0.93–1.29)	0.243
HOMA-R (1 pg/mL)	0.99 (0.68–1.41)	0.969

Abbreviations are as shown in Table 1. *p<0.05

Table 4: Predictors of MACCEs by multivariate Cox regression analyses.

This study supposes that IL-6 is useful tool to identify high-risk patients for cardiovascular events. However, ESTHER study [15] reported that IL-6 did not substantially improve risk prediction above traditional risk factors in a diabetic cohort. Subjects in ESTHER study had much greater BMI than those in the present study (29.1 vs. 25.4 kg/m^2). The discrepancy may be explained by the difference of study population, because some studies reported that serum IL-6 levels were strongly associated with BMI [29,30].

This study had several limitations. Firstly, subjects in the study population had essential hypertension and dyslipidemia. Most of them were treated with anti-hypertensive or statin drugs. These drugs have been reported to have anti-inflammatory effects [31-33]. Our small cross-sectional study did not allow us to statistically analyze and exclude the potential effects of these influences. Secondly, we relied upon single measurements of IL-6. We did not examine the change in serum IL-6 levels during follow-up. The prognostic potential of IL-6 may be increased by serially evaluating its levels. Finally, because we enrolled patients without severe complications, the incidence of MACCE was small. The HR values in the present study were not high. The number of patients in this study may not be enough to conclude safe results about the incidence of MACCE in T2DM patients. Therefore, further studies are necessary to clarify the significance of IL-6 levels for determining the prognosis of T2DM patients.

Conclusion

The present study demonstrated that an elevated serum IL-6 level at baseline has long-term predictive value for assessing CVD in patients with T2DM without structural heart disease. Measurement of serum concentrations of IL-6 is a useful tool to identify high-risk patients for cardiovascular events. Intensive management should be considered in high IL-6 patient groups.

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