Soluble L-Selectin Level Is a Marker for Coronary Artery Disease in Type 2 Diabetic Patients

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OBJECTIVE — To investigate whether the fall in soluble L-selectin (sL-selectin) level constitutes a marker for myocardial ischemia.

RESEARCH DESIGN AND METHODS — The levels of soluble forms of adhesion molecules, i.e., intercellular adhesion molecule-1 (sICAM-1), vascular cell adhesion molecule-1 (sVCAM-1), E-selectin (sE-selectin), P-selectin (sP-selectin), and L-selectin (sL-selectin), were compared in type 2 diabetic patients without inflammatory syndrome but with symptomatic coronary artery disease (CAD) (group 1, n = 11), with silent ischemic disorders and proven coronary stenoses (group 2, n = 11), with silent myocardial ischemia (SMI) and normal coronary angiography (group 3, n = 10), and without proven SMI (group 4, n = 13). These levels were compared with those of 22 control subjects.

RESULTS — The sL-selectin level was significantly lower in groups 1, 2, or 3 with symptomatic CAD or with SMI as compared with the control group (P = 0.0004). Group 4 without myocardial ischemia did not significantly differ from the control subjects (P = 0.6). In type 2 diabetic patients, after controlling for HbA_{1c}, a partial correlation between sL-selectin and the CAD status was significant (P = 0.001). sICAM-1 and sP- or sE-selectin did not differ significantly between type 2 diabetic patients and control subjects or among the different groups of patients. The sVCAM-1 level in type 2 diabetic patients was significantly higher than in the control subjects (P = 0.001), but there were no significant intergroup differences (P = 0.4).

CONCLUSIONS — In type 2 diabetic patients, sVCAM-1 is increased with regard to glycemic control, whatever the CAD status. In type 2 diabetic patients with symptomatic CAD or SMI associated with coronary stenoses, sL-selectin is significantly decreased. A marked fall in sL-selectin might constitute a marker for silent CAD in type 2 diabetic patients.

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Both the role of endothelium as a primary target organ for atherosclerosis (1) and the involvement of adhesion molecules in the genesis of macroangiopathic complications of diabetes have been suggested (2). Inflammation or thrombosis lead to activation of the endothelium, which displays adhesion molecules. These molecules bind free-flowing leukocytes, slowing them down and causing them to roll along with bloodstream under hydrodynamic shear stress through labile contacts with the endothelium cells (3). Initial contact (tethering) and rolling are mediated by L-, E- and P-selectins (4), which belong to the family of adhesion proteins. At a higher flow rate (5), the L-selectin (CD62L) expressed on leukocyte subsets is involved in the prerequisite step for the leukocyte to roll along vascular endothelium at sites of inflammation. After induction via the nuclear factor κB (NF-κB) pathway, E-selectin (CD62E) expressed on inflammatory cytokine-activated endothelial cells is also involved in leukocyte migration (6). P-selectin (CD62P) is expressed by endothelial cells and platelets (7). Transient rolling on the vessel wall is converted into firm adhesion by intercellular adhesion molecule-1 (ICAM-1) (CD54) and/or by vascular cell adhesion molecule-1 (VCAM-1) (CD106), two inducible integrins belonging to the immunoglobulin superfamily.

More than half of diabetic patients die of coronary artery disease (CAD), and because myocardial infarction often occurs silently (8), early detection of CAD may be of clinical importance. Studies focusing on strictly asymptomatic diabetic patients have been performed to detect silent myocardial ischemia (SMI). Using noninvasive tests, SMI was found in 20–30% of strictly asymptomatic diabetic patients with one or two additional cardiovascular risk factors (9–12). About one-third of these patients had significant coronary stenoses (10,12). However, in the other patients, a defect in coronary endothelial-dependent vasodilatation or in the coronary reserve could account for a positive noninvasive test (13). Therefore, a relevant seric marker for CAD might be of major clinical value to identify patients liable to SMI. Because adhesion molecules are involved in atherosclerosis and cardiovascular diseases, their soluble forms might be potential markers.

Plasma levels of some soluble adhesion molecules have been studied in various inflammation and/or thrombosis activation disorders. An increase in soluble VCAM-1 (sVCAM-1) and soluble ICAM-1 (sICAM-1) has been reported in CAD (14) and in acute myocardial infarction (AMI) (15). An increase in soluble P-selectin (sP-selectin) has also been reported in atherosclerosis

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Abbreviations: AMI, acute myocardial infarction; ANCOVA, analysis of covariance; ANOVA, analysis of variance; CAD, coronary artery disease; CRP, C-reactive protein; ECG, electrocardiogram; sE-selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1; sL-selectin, soluble L-selectin; SMI, silent myocardial ischemia; sP-selectin, soluble P-selectin; sVCAM-1, soluble vascular cell adhesion molecule-1.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

(16). Few data are available on soluble L-selectin (sL-selectin) changes. As observed in AMI and angina pectoris, the sL-selectin low level may be related to a depressed expression (14).

Significantly elevated levels of soluble E-selectin (sE-selectin) (17,18), sICAM-1 (19), and sVCAM-1 (17) have been reported in type 2 diabetes, whereas sL-selectin level was neither modified nor related to glycemic control (17; J.-P.A., P.V., unpublished observations).

The purpose of the present study was to investigate whether soluble adhesion molecules are reliable markers for CAD and help detect SMI in type 2 diabetes.

RESEARCH DESIGN AND METHODS

Patients

A total of 45 type 2 diabetic patients were studied. None had acute or chronic inflammatory disease, confirmed by C-reactive protein (CRP) and orosomucoid measurements. These patients were divided into four groups. Group 1 (n = 11) was characterized by symptomatic CAD: patients suffering from stable angina pectoris with significant stenoses on angiography or with a history of myocardial infarction or coronary artery bypass that had occurred >6 months ago. Previously, patients in groups 2, 3, and 4 were investigated for SMI (12). For these three groups, the criteria for inclusion were absence of myocardial infarction or angina pectoris, a normal 12-lead electrocardiogram (ECG), diabetes duration >5 years, and presence of at least two additional cardiovascular risk factors. These factors were dyslipidemia (total cholesterol >6.5 mmol/l and/or triglycerides >2.8 mmol/l), arterial hypertension (blood pressure >140/90 mmHg [20]), obesity (BMI >29 kg/m^2), tobacco consumption, lower limb obstructive arterial disease, nephropathy defined by a urinary albumin excretion rate >30 mg/day, and a family history of early cardiovascular disease. Three methods were used to detect SMI: an ECG stress test, a thallium 201 myocardial scintigraphy with intravenous infusion of dipyridamole, and/or a 48-h ambulatory ECG monitoring. Coronary angiography was proposed to the patients who had one positive noninvasive test. Coronary stenosis was considered to be significant when there was ≥50% narrowing on the left coronary artery or ≥70% narrowing on the left anterior descending artery, on the circumflex, on a well-developed marginal vessel, or on the right coronary artery. In group 2 (n = 11), patients showed SMI on noninvasive tests, and significant coronary stenoses were found on angiography. Group 3 (n = 10) also showed SMI, but the coronary angiography was normal according to two independent investigators. In group 4 (n = 13), patients were free of SMI, and the three noninvasive tests were normal.

Patients were informed and signed consent to participate in the assessment of SMI. This study received the approval of the Ethical Committee of Reims (France). Clinical parameters are shown in Table 1. Diabetic retinopathy was assessed by fundus ophthalmoscopy. Patients who had smoked regularly for the previous 12 months were classified as current smokers. Hypertensive patients were treated by an angiotensin enzyme inhibitor, a calcium channel blocker, or a β-blocker.

According to clinical and biological criteria, 22 HIV seronegative healthy volunteer blood donors of the Blood Transfusion Center of Seine Saint-Denis, France (14 men, 8 women, mean age 48 ± 4.5 years) were selected and studied as control subjects (group 5). They met the following exclusion criteria: inflammatory disorder, dyslipoproteinemia, cardiovascular disease, known diabetes or other endocrine disorders, hepatic or renal failure, overweight, smoking, alcohol consumption, hypertension, and/or therapy known to cause changes in the lipoprotein profile (e.g., estrogen treatment). Some exclusion criteria were extended to the ascendants: cardiovascular disease, known diabetes or other endocrine disorders, and dyslipoproteinemia.

Analytical methods

Adhesion glycoproteins. All tests were performed using frozen serum collected at fasting and stored at −80°C. sICAM-1, sVCAM-1, sE-selectin, sP-selectin, and sL-selectin levels were assessed with an enzyme-linked immonosorbent assay using monoclonal antibodies specific for each of these adhesion molecules (R&D Systems, Abingdon, Oxfordshire, U.K.). The lower limits of detection of these assays were 0.35, 2, 0.1, 0.5, and 0.5 ng/ml, respectively. The standards covered a range of 2–47, 4–76, 0.5–10, 1–5, and 1.2–55 ng/ml, respectively. Three sera were assayed in 10 replicates and the intra-assay precision was assessed by the coefficient of variation, which was 4.8, 5, 4.8, 5.2, and 3.5%, respectively. Three sera were assayed in duplicate in 6–14 separate assays, and the inter-assay precision was assessed by the coefficient of variation, which was 7.4, 9, 7.3, 8.8, and 6.6, respectively. Sera were diluted and assayed in duplicate. The assay of CRP had a lower limit of detection of 0.7 mg/l, and normal values were ≤5 mg/l. Normal values of orosomucoid were 0.5–1.2 g/l.

Biochemical parameters. Total cholesterol, triglycerides, and blood glucose concentrations were measured by automated enzymatic methods. HDL cholesterol was similarly measured after precipitation of other lipoprotein classes with phosphotungstic acid and magnesium chloride. LDL cholesterol was calculated by the Friedwald formula. Serum CRP and orosomucoid were determined by immunonephelometric assay on Behring Nephelometric Analyzer (Behring, Marburg, Germany). HbA_{1c} was assessed by microcolumn chromatography (Bio-Rad, Hercules, CA) and fructosamine by a colorimetric test with nitroblue tetrazolium (Roche-Diagnostic, Basel, Switzerland). Plasma insulin and C-peptide levels were determined by radioimmunoassay (RIA-gnost, Behring).

Statistical methods. Results are summarized as mean ± SEM or median (interquartile range 25–75%). Because of the skewed distribution of soluble adhesion molecules, differences in concentration were evaluated through nonparametric statistical procedures (Mann-Whitney U and Kruskal-Wallis tests). Analyses of variance (ANOVA) and covariance (ANCOVA) were performed to examine a possible relationship among sL-selectin, CAD status, sex, and age. Multivariate logistic regression used the backward stepwise likelihood ratio procedure with an entrance P value of ≤0.05 for inclusion. Correction for multiple comparisons was not performed in the present study. A two-sided probability value of <0.05 was considered significant.

RESULTS — Significant differences in HbA_{1c}, fructosamine, triglycerides, and LDL cholesterol levels were observed among the groups of type 2 diabetic patients (Table 1). Values of sICAM-1, sP-selectin, and sE-selectin were not significantly different in the control subjects and in the four groups of type 2 diabetic patients (Table 2). sVCAM-1 levels were significantly higher in the type 2 diabetic patients, whereas no significant intergroup difference was observed (P = 0.0008) (Table 2).

Significant differences in sL-selectin values among the five groups (P = 0.0004) and

Table 1—*Clinical and biological parameters in the four groups of type 2 diabetic patients*

	Group 1	Group 2	Group 3	Group 4	*P* (Kruskall-Wallis)
n	11	11	10	13	—
Sex (M/F)	8/3	9/2	7/3	5/8	—
Age (years)	65 ± 6	65 ± 6	54 ± 10	53 ± 11	—
Hypertension	7 (64)	10 (91)	9 (90)	9 (69)	—
Hyperlipidemia	6 (55)	9 (82)	5 (50)	8 (62)	—
Lower limb arteriopathy	5 (45)	2 (18)	2 (20)	1 (8)	—
Nephropathy	6 (55)	4 (36)	2 (20)	1 (8)	—
Retinopathy	2 (18)	6 (55)	2 (20)	1 (8)	—
Family atherosclerosis	0	2 (18)	5 (50)	7 (54)	—
Smoking (current)	5 (45)	7 (64)	5 (50)	5 (38)	—
Alcoholic addiction	0	2 (18)	1 (10)	1 (8)	—
Glycemia (mmol/l)					
Fasting	9.6 ± 1.1	8.6 ± 1.1	8.7 ± 0.8	8.4 ± 0.8	NS
Postprandial (2:00 P.M.)	15.3 ± 1.7	13.7 ± 1.8	11.0 ± 1.6	12.0 ± 1.5	NS
Plasma insulin (pmol/l)					
Fasting	75 ± 9	78 ± 15	90 ± 15	84 ± 19	NS
Postprandial (2:00 P.M.)	260 ± 45	504 ± 140	340 ± 85	259 ± 70	NS
Plasma C-peptide (pmol/l)					
Fasting	738 ± 95	726 ± 90	577 ± 95	686 ± 86	NS
Postprandial (2:00 P.M.)	1,850 ± 250	1,520 ± 350	1,120 ± 220	1,465 ± 210	NS
HbA_{1c} (%)	8.9 ± 0.8	9.7 ± 0.9	8.8 ± 0.5	6.3 ± 0.3	0.003
Fructosamine (μmol/l)	320 ± 23	384 ± 20	383 ± 32	306 ± 15	0.03
Total cholesterol (mmol/l)	5.4 ± 0.4	5.6 ± 0.3	5.1 ± 0.2	6.0 ± 0.3	NS
Triglycerides (mmol/l)	2.4 ± 0.3	2.1 ± 0.3	1.3 ± 0.1	1.6 ± 0.2	0.008
HDL cholesterol (mmol/l)	1.1 ± 0.1	1.4 ± 0.2	1.6 ± 0.1	1.4 ± 0.1	0.03
LDL cholesterol (mmol/l)	4.3 ± 0.4	3.4 ± 0.4	3.1 ± 0.1	4.1 ± 0.5	0.05

Data are means ± SD or *n* (%), unless otherwise indicated. The clinical definitions have been included in RESEARCHDESIGNANDMETHODS .

in the four groups of type 2 diabetic patients ($P = 0.01$) were observed. In groups 1, 2, and 3 with SMI or symptomatic myocardial ischemia, the sL-selectin level was significantly lower than in the control group (Table 2). The sL-selectin level was also lower in groups 1 and 2 (with proven coronary stenoses) than in group 4 (SMI absent). No difference among groups 1, 2, and 3 or between group 4 and the control group was observed. However, a trend (NS) to decreased sL-selectin was observed in group 3 (with SMI but normal coronary angiography) when compared with group 4 (Table 2). No significant effects of sex and age on sL-selectin levels were respectively observed by ANOVA ($P = 0.3$) and ANCOVA ($P = 0.4$). However, ANOVA confirmed the main effect of the CAD status on sL-selectin levels ($P = 0.004$). Furthermore, after controlling for HbA_{1c} or age, the sL-selectin level partially correlated with the CAD status ($P = 0.001$ and 0.01, respectively). Groups 1 and 2 (either symptomatic or silent CAD) did not significantly differ in their sL-selectin levels. Therefore, these two groups were pooled to operate logistic regression (hence, $n = 22$). In this procedure, the dependent variable was the CAD status in groups 1, 2, or 4, coded as yes or no. The logistic regression model first included sL-selectin, HbA_{1c}, fructosamine, LDL cholesterol, and triglycerides as potential independent predictors. Stepping backward from this full model resulted in the removal of fructosamine, LDL cholesterol, and triglycerides. The final multivariate model, which included sL-selectin and HbA_{1c}, showed that these two parameters were independently associated with the CAD status (Table 3). The crude and adjusted odds ratios were quite similar (Mantel-Haenszel test) for sL-selectin either in groups 1 and 2 versus the control group or in groups 1 and 2 versus group 4.

CONCLUSIONS — The present study demonstrates that sL-selectin levels in type 2 diabetic patients with symptomatic CAD or

Table 2—*Soluble adhesion protein levels in type 2 diabetic patients and control subjects*

	Group 1	Group 2	Group 3	Group 4	Control group
n	11	11	10	13	22
sL-selectin (ng/ml)	983 ± 52§¶	1,070 ± 70‡‖	1,190 ± 87*	1,404 ± 95	1,390 ± 45
sE-selectin (ng/ml)	58 ± 10	71 ± 11	59 ± 5	77 ± 8	50 ± 5
sP-selectin (ng/ml)	201 ± 26	195 ± 31	220 ± 30	195 ± 25	157 ± 18
sICAM-1 (ng/ml)	230 ± 12	280 ± 40	245 ± 36	254 ± 21	247 ± 19
sVCAM-1 (ng/ml)	874 ± 98‡	627 ± 26†	650 ± 40†	696 ± 82†	550 ± 35

Data are means ± SD. *$P = 0.03$, †$P < 0.01$, ‡$P = 0.002$, §$P < 0.0001$ when compared with the control group; ‖$P = 0.02$ and ¶$P = 0.005$ when compared with the SMI absent group.

Table 3—*Logistic regression with CAD status as the dependent variable*

Variable	Wald	*P* (Wald)	Partial *r*	Adjusted odds ratio (95% CI)	Crude odds ratio (95% CI)
Final multivariate model (groups 1 and 2 vs. group 4)					
L-selectin (ng/ml)	3.83	0.050	0.206	1.004 (1.002–1.006)	1.005 (1.001–1.008)
HbA_{1c} (%)	3.94	0.047	−0.212	0.475 (0.326–0.690)	0.432 (0.225–0.830)
Constant	0.003	0.96	—	—	—
Univariate model (groups 1 and 2 vs. group 5)					
L-selectin (ng/ml)	12.30	0.0005	0.410	—	1.007 (1.003–1.012)

with SMI are significantly lower than those in control subjects. No difference was observed between diabetic patients without SMI and control subjects. No influence of sex or age on sL-selectin levels was found in any of the type 2 diabetic patients.

A comparison of the four groups of type 2 diabetic patients revealed no significant difference in the clinical parameters, particularly for peripheral arterial disease, but HbA_{1c}, fructosamine, triglycerides, HDL cholesterol, and LDL cholesterol significantly differed. According to multivariate analysis, sL-selectin levels appeared to be significantly associated with the CAD status, independently of the metabolic parameters. The lower sL-selectin level in type 2 diabetic patients with symptomatic CAD (group 1) and in patients with SMI and coronary stenoses (group 2) as compared with patients without SMI (group 4) was in accordance with Haught's report on nondiabetic patients suffering from stable or unstable angina pectoris or AMI (14). Similarly, the present study clearly shows a significant fall in the sL-selectin level in type 2 diabetic patients with SMI as compared with those free of any sign of SMI and with the control subjects. The trend (NS) to a decreased sL-selectin level in patients with SMI but with a normal angiography (group 3) as compared with patients without SMI (group 4) suggests that a sL-selectin decrease might be a marker for coronary stenoses. In such type 2 diabetic patients with SMI with a normal angiography, we found evidence of a reduced endothelial-dependent vasomotricity in epicardic coronary arteries and the microcirculatory coronary reserve related to oxygen-free radical accumulation (13,21). Therefore, the slight decrease in sL-selectin might be an index of endothelial dysfunction. Further confirmation of our data on a larger series of patients is the aim of a prospective study currently underway. The fact that the sL-selectin level did not significantly differ between patients suffering from symptomatic CAD (group 1) or SMI with stenoses (group 2) further demonstrates that sL-selectin might be a marker for silent coronary stenoses.

We observed that the sVCAM-1 level was significantly higher in the four groups of type 2 diabetic patients than in the control subjects. Whatever the cardiovascular status, no significant intergroup difference was observed between these patients. We had previously observed the fall of sVCAM-1 in poorly controlled type 2 diabetic patients after a 14-day intensive insulin treatment (17). Taken together, these data strongly suggest that diabetes-associated metabolic disorders can explain the significant enhancement of the sVCAM-1 level. The levels of sICAM-1 or sP-selectin were not significantly different in the type 2 diabetic patients with symptomatic CAD or SMI and the control subjects.

L-selectin mediates tethering and the first step of leukocyte rolling. The soluble form of L-selectin is released by a rapid shedding from the cell surface (22). Walcheck et al. (23) have reported that hydroxamic acid–based metalloprotease inhibitors block L-selectin downregulation from the cell surface of stimulated neutrophils and inhibit the neutrophil rolling velocity under hydrodynamic flow, leading to an increased neutrophil accumulation. Therefore, shedding may limit leukocyte aggregation and accumulation.

In the present study, the fall in the sL-selectin level observed in type 2 diabetic patients with CAD or SMI may be related to decreased L-selectin shedding from circulating leukocytes, followed by an increased attachment of leukocytes to activated endothelium. This decrease might be ascribed to a downregulation of L-selectin cellular expression correlated to a low-grade inflammatory process because type 2 diabetes is a chronic inflammatory disease with consequent atherosclerosis.

Because increased sE-selectin levels have been reported (18) in poorly controlled type 2 diabetic patients, the normal levels observed here, in agreement with other reports (24), may be related to a decreased shedding in cardiovascular disease.

In conclusion, in type 2 diabetic patients without inflammatory syndrome, sVCAM-1 is increased with regard to glycemic control, whatever the CAD status. In these type 2 diabetic patients with symptomatic CAD or SMI and coronary stenoses, sL-selectin is significantly decreased. This indicates that a marked decrease of sL-selectin might be used as a predictive marker of coronary stenoses in diabetic patients.

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