

Elevated Concentrations of Soluble E-Selectin and Vascular Cell Adhesion Molecule-1 in NIDDM

Effect of intensive insulin treatment

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OBJECTIVE — To evaluate the effects of a 14-day intensive insulin therapy and short-term improvement of glycemic control on serum levels of soluble forms of adhesion molecules, i.e., intercellular adhesion molecule-1 (sICAM-1), vascular cell adhesion molecule-1 (sVCAM-1), and E-selectin (sE-selectin) in NIDDM patients with poor glycemic control.

RESEARCH DESIGN AND METHODS — A total of 16 NIDDM patients were compared with 23 healthy subjects (control group) and investigated before and after intensive insulin treatment.

RESULTS — On day 0, sE-selectin and sVCAM-1 levels were significantly higher in NIDDM patients than in nondiabetic control subjects (median 87, range 63–115; median 544, range 408–797 vs. 58, 43–80; 443, 395–573 ng/ml, respectively) ($P < 0.008$ in both cases). On day 15, the fall in sE-selectin levels was significant ($P < 0.0001$) and at a lesser extent in sVCAM-1 levels (64, 48–85; 506, 417–678 ng/ml, respectively); these levels reached values that no longer differed from those of control subjects ($P = 0.23$ and 0.15 , respectively). Moreover, the fall in sE-selectin was positively associated with the change in LDL cholesterol and the improvement of glycemia.

CONCLUSIONS — In poorly controlled NIDDM patients, sE-selectin levels are increased and significantly fall to normal after short-term improvement of glycemic control. This suggests that assaying sE-selectin makes it possible to detect endothelium activation and to follow its reversal with euglycemia.

Diabetes is associated with an increased risk for cardiovascular events (1). Endothelial dysfunction precedes the development of atherosclerosis in NIDDM patients (2). The possible role of adhesion molecules in atherosclerosis has been suggested (3). Intercellular adhesion molecule-1 (ICAM-1, CD54) and vascular cell adhesion molecule-1 (VCAM-1, CD106)

are related molecules belonging to the immunoglobulin supergene family (4,5). These molecules are ligands for leukocyte integrins and are thought to stabilize the adhesion of leukocytes to endothelium and to be involved in cellular interactions within the tissues (6–8). The expression of ICAM-1 is not restricted to endothelial cells but has also been demonstrated on lymphocytes,

monocytes, and various types of non-hematopoietic cells (7). VCAM-1 was thought to be expressed only by endothelial cells. However, it is also found on nonendothelial cells, including lymphoid dendritic cells, tissue macrophages, and renal tubular epithelial cells (9). On the other hand, E-selectin (CD62E) is only found on activated endothelium in contrast to other adhesion molecules characterized by a wider tissue distribution (10). Endothelial cells release E-selectin after *in vitro* activation. Interactions between E-selectin and VCAM-1 and their ligands may, in part, underlie the phenomenon of leukocyte rolling on the vessel wall at sites of inflammation (11). Soluble forms of E-selectin (sE-selectin), VCAM-1 (sVCAM-1), and ICAM-1 (sICAM-1) have been detected in blood from normal subjects. Some of these soluble forms are significantly increased in sera from patients with different inflammatory or malignant diseases and in diabetes. Advanced glycation end products (AGEs) have recently been shown to increase the expression of sVCAM-1 and sE-selectin (12). It is likely that the soluble forms of these adhesion molecules are derived from the corresponding component expressed on the surface of activated cells (13). In NIDDM, Cominacini et al. (14) have reported, for a small sample ($n = 13$), increased sE-selectin and sICAM-1 levels, while sVCAM-1 concentrations did not differ from those observed in healthy control subjects; moreover, serum E-selectin positively correlated with the GHb level but not with the concentration of serum lipids. Fasching et al. (15) showed, on a larger sample ($n = 159$), a weak correlation between sE-selectin and HbA_{1c}. Previously, Steiner et al. (16) reported significantly elevated levels of sE-selectin and sVCAM-1 and normal levels of sICAM-1 in NIDDM patients compared with healthy control subjects. In their study, the elevated levels of adhesion molecules did not correlate with glycemic control but correlated weakly with LDL cholesterol. More recently, Cominacini et al. (17) have shown that sE-selectin levels

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Abbreviations: AGE, advanced glycation end product; apo, apolipoprotein; CRP, C-reactive protein; CSII, continuous subcutaneous insulin infusion; ICAM-1, intercellular adhesion molecule-1; Lp(A1), lipoparticle A1; OR, odds ratio; sE-selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.

Table 1—Clinical characteristics of the 16 NIDDM patients on day 0

Age (years)	55.2 ± 2.3
Sex (M/W)	8/8
Duration of diabetes (years)	11.2 ± 2.1
Body weight (kg)	78.5 ± 3.3
BMI (kg/m ²)	28.9 ± 1.1
Hypertension	4
Incipient nephropathy	6
Lower limb arteropathy	5
Coronary heart disease	6
Peripheral neuropathy	12
Fundus ophthalmoscopy retinopathy	4

Data are means ± SEM or *n*. The clinical definitions have been included in METHODS.

decrease in NIDDM patients after a 90-day period of glycemic improvement. As previously shown (1,2), blood glucose levels, GHb, dyslipidemia, and diabetes-associated atherosclerosis correlated. The purpose of this study was to determine sE-selectin, sVCAM-1, and sICAM-1 levels in NIDDM patients with poor glycemic control despite maximal oral hypoglycemic treatment compared with those in healthy subjects and their changes after obtaining good glycemic control by a 14-day intensive insulin treatment with continuous subcutaneous insulin infusion (CSII) as previously described (18).

RESEARCH DESIGN AND METHODS

Patients

Sixteen NIDDM patients (islet cell antibodies negative and fasting plasma C-peptide >600 pmol/l) with a mean (± SD) duration of diabetes of 11.2 (± 2.1) years were studied. Clinical characteristics are shown in Table 1. Hypertension was defined as blood pressure >160/90 mmHg. Incipient nephropathy was defined as a urinary albumin excretion rate between 30 and 300 mg/24 h. Five patients had distal lower limb arterial disease confirmed by an artery ultrasound examination without trophic wound. Silent myocardial ischemia was defined by a positive stress electrocardiogram test or myocardial thallium scintigraphy with dipyridamole administration. Peripheral neuropathy was confirmed by neurophysiological examination. The patients had poor metabolic control (HbA_{1c} = 9.5 ± 0.5%) despite maximal oral antidiabetic treatment with glibenclamide 15 mg/day and met-

formin 1,700 mg/day and a low-calorie diet (1,000–1,200 kcal). None had hepatic or renal failure or infectious or inflammatory disease, confirmed by C-reactive protein and orosomuroid measurements. None of the patients were taking aspirin or anticoagulant and none of the women were treated by estrogens. Four patients were hypertensive: one patient was treated by captopril, which is known to have no significant antioxidant activity in human plasma (19) despite the presence of a thiol group, and the other three were treated either by a calcium blocker or by a β-blocker. In all of them, hypertension was controlled during the time of investigation. These treatments were continued during the study. Three patients were active smokers, four were ex-smokers, and the others were nonsmokers.

Sera from 23 HIV seronegative healthy adults (17 men, 6 women, mean age 50 [± 3.1] years) were chosen from the sera of nonretributed blood donors of the Blood Transfusion Center of Seine St. Denis, France and studied as control subjects because 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, hypertensive status, and/or therapy known to cause changes in lipoprotein profile, such as an estrogen treatment. Some exclusion criteria were extended to the ascendants: cardiovascular disease, known diabetes or other endocrine disorders, dyslipoproteinemia.

Study design

All patients were hospitalized for a 3-week period. Metabolic control was poor, despite maximal oral treatment, and remained poor after 3 days of a controlled low-calorie diet, which consisted of a 40% reduction of the usual calorie intake. Glibenclamide was withdrawn. The same low-calorie diet (1,000–1,200 kcal/day: 50% carbohydrates, 30% lipids, 20% proteins) and 1,700 mg/day metformin were maintained.

CSII was started in the morning, using an MKII infuser (Novo Nordisk, Boulogne-Billancourt, France) and regular insulin (Velosulin). Meals were taken at 8:00 A.M., 12 noon, and 5:00 P.M. Optimal glycemic control was obtained by the second day of CSII, with the total insulin rate at 0.55 U · kg⁻¹ · day⁻¹, including preprandial bolus. CSII was maintained for a 14-day period and was stopped on the evening before the

last day. A lower dose of glibenclamide (7.5 mg/day) was then given the following day.

Analytical methods

Adhesion glycoproteins. All tests were performed using frozen serum collected, at baseline, from all subjects and from patients after treatment, at day 15, and stored at –20°C for up to 2 months. Moreover, we verified on several aliquots that these conditions of storage did not induce any change in the different adhesion glycoprotein levels. sICAM-1, sVCAM-1, and sE-selectin levels were determined with enzyme-linked immunosorbent assay using monoclonal antibodies specific for each of these adhesion molecules (R & D Systems, Abingdon, Oxfordshire, U.K.). The lower limits of detection were 0.35, 2, and 0.1 ng/ml, respectively, with standards covering a range of 2–47, 4–76, and 0.5–10 ng/ml for sICAM-1, sVCAM-1, and sE-selectin, respectively. Sera were diluted and assayed in duplicate.

Biochemical parameters. Blood glucose control was assessed by fasting blood glucose concentration (automated glucose oxidase method), HbA_{1c} by microcolumn chromatography (Bio-Rad, Hercules, CA), and fructosamine by a colorimetric test with nitroblue tetrazolium (Roche, Basel, Switzerland). Plasma insulin and C-peptide levels were determined, in duplicate, by radioimmunoassay (RIA-gnost; Behring Institute, Marburg, Germany). On the same days, glycemia, plasma insulin, and C-peptide were measured from samples taken at 8:00 A.M. (fasting), 12 noon, 2:00 P.M., 4:00 P.M., 6:00 P.M., 9:00 P.M., 12 midnight, and 4:00 A.M. The mean value for these measurements was calculated. Total cholesterol, HDL cholesterol, triglycerides, apolipoprotein (apo) A1, and apo B were determined on fresh samples. Cholesterol and triglycerides were measured by automated enzymatic methods, CHOD-PAP and GPO-PAP, respectively (Roche). HDL cholesterol was similarly measured after precipitation of other lipoprotein classes with phosphotungstic acid and magnesium chloride. Apo A1 and apo B were measured by immunoturbidimetry with specific antibodies (Roche). Lipoparticle A1 (Lp[A1]) was measured by immunodiffusion on hydragel using a kit supplied by Sebia (Issy-les-Moulineaux, France). Serum C-reactive protein (CRP) and orosomuroid were determined by immunonephelometric assays on Behring Nephelometric Analyzer (Behring, Marburg, Germany) with N-Latex CRP or orosomuroid kits (Behring). Normal

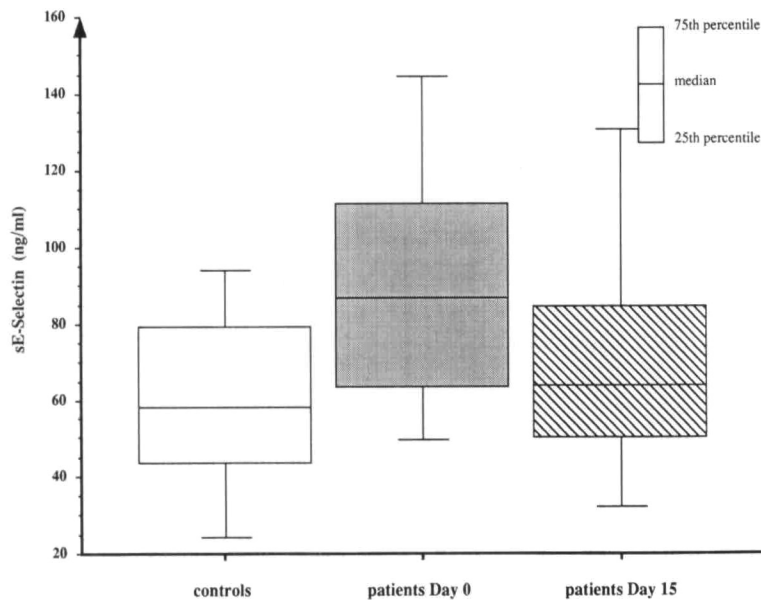


Figure 1—Serum levels of sE-selectin in 23 healthy control subjects and 16 NIDDM patients before (day 0) and after (day 15) CSII. The difference between the patients and the healthy subjects is significant at day 0 ($P = 0.008$) but not at day 15.

values are ≤ 5 mg/l and 1.40 g/l for CRP and orosomucoid, respectively.

Statistical methods

Statistical analysis was performed using the SPSS program, version 6.1 for Power Macintosh. Results are summarized as means \pm SE or median (interquartile range of 25–75%). Because of the skewed distribution of soluble adhesion molecules, differences in concentrations were evaluated through nonparametric statistical procedures (Mann-Whitney U and Kruskal-Wallis tests). When using parametric procedures, values were transformed into natural logarithms to approach normal distribution. Correlation coefficients between two sets of quantitative data were calculated as either the Pearson product-moment or Spearman's rank correlation coefficient. Multivariate logistic regression used the backward stepwise likelihood-ratio procedure and an entrance P value of ≤ 0.05 for inclusion. For all analyses, a two-sided probability value of < 0.05 was considered significant. Correction for multiple comparisons was not performed in any of the analyses in the present study.

RESULTS

Changes in adhesion glycoproteins

Values of sE-selectin in the 23 healthy adults ranged from 43 to 80 ng/ml with a median of 58 ng/ml. On day 0, serum con-

centrations of the NIDDM patients ranged from 63 to 115 ng/ml with a median of 87 ng/ml (Fig. 1). The difference between patients and the control group was significant (with logarithm-transformed values, $P = 0.008$). On day 15, after insulin treat-

ment, values of sE-selectin were significantly lower ($P < 0.0001$, paired Student's t test with logarithm-transformed values), ranging from 48 to 85 ng/ml with a median of 64 ng/ml, and no longer differed significantly from the values observed for the healthy control subjects (Fig. 1).

Values of sVCAM-1 in the 23 healthy adults ranged from 395 to 573 ng/ml with a median of 443 ng/ml. On day 0, serum concentrations in the NIDDM patients with poor glycemic control before insulin treatment ranged from 408 to 797 ng/ml with a median of 544 ng/ml. The difference between the patients and the control group was significant ($P = 0.008$, with logarithmic values). On day 15, after insulin treatment, the values of sVCAM-1 were lower, ranging from 417 to 678 ng/ml with a median of 506 ng/ml; these values did not differ significantly from the values observed in the control group.

Values of sICAM-1 in the 23 healthy adults ranged from 193 to 289 ng/ml with a median of 226 ng/ml. On day 0, serum concentrations in NIDDM patients with poor glycemic control before insulin treatment ranged from 199 to 267 ng/ml with a median of 216 ng/ml. The difference between the patients and the control group was not significant. On day 15, after insulin treat-

Table 2—Biological parameters in the 16 NIDDM patients at day 0 (before CSII) and just after the withdrawal of CSII (day 15) and in the 23 control subjects

	Day 0	Day 15	Control group
Glycemia (mmol/l)			
Fasting	12.2 \pm 0.7*	7.6 \pm 0.4*	4.9 \pm 0.9*
Postprandial (2:00 P.M.)	13.7 \pm 1.2*	9.4 \pm 1.0*	—
Mean	12.0 \pm 1.1	8.3 \pm 0.6	—
HbA _{1c} (%)	9.6 \pm 0.4*	—	5 \pm 0.8*
Plasma insulin (pmol/l)			
Fasting	80 \pm 8*	57 \pm 4*	80 \pm 10
Postprandial (2:00 P.M.)	203 \pm 22	211 \pm 22	—
Mean	114 \pm 10	101 \pm 9	—
Plasma C-peptide (pmol/l)			
Fasting	825 \pm 65*	650 \pm 60*	610 \pm 60
Postprandial (2:00 P.M.)	1,713 \pm 121	2,095 \pm 179	—
Mean	1,082 \pm 81.2	1,096 \pm 91	—
Total cholesterol (mmol/l)	5.6 \pm 0.3*	4.6 \pm 0.3*	5.2 \pm 0.3
Triglycerides (mmol/l)	1.9 \pm 0.2*	1.1 \pm 0.1*	1.1 \pm 0.1
HDL cholesterol (mmol/l)	1.0 \pm 0.1	1.1 \pm 0.1	1.3 \pm 0.2
LDL cholesterol (mmol/l)	4.1 \pm 0.3*	3.3 \pm 0.3*	2.8 \pm 0.2
Apo A ₁ (g/l)	1.5 \pm 0.1*	1.2 \pm 0.1*	1.3 \pm 0.2
Apo B (g/l)	1.2 \pm 0.1*	1.0 \pm 0.1*	1.0 \pm 0.1
Lp(A1) (g/l)	0.5 \pm 0.03	0.5 \pm 0.02	0.4 \pm 0.02

Data are means \pm SEM. Mean values are for eight measurements over a day. *Significant difference (at least $P < 0.05$).

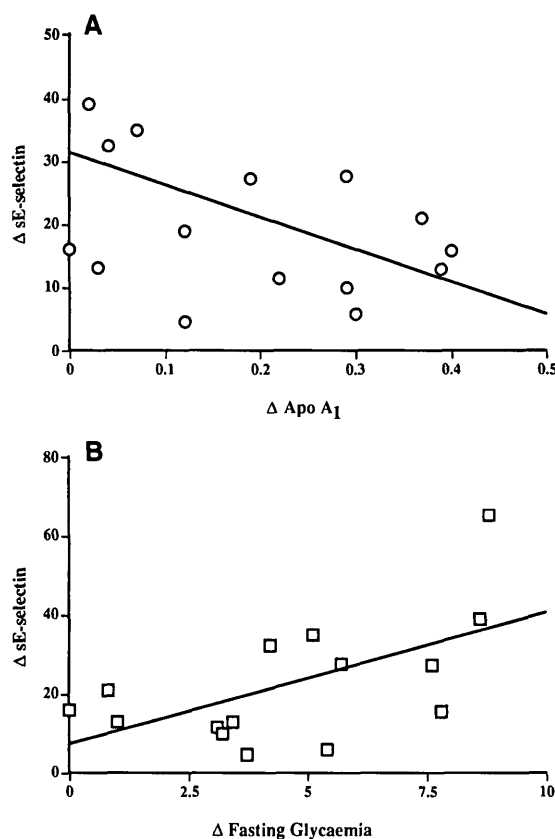


Figure 2—Fall in sE-selectin between day 0 and day 15 versus change in apo A₁ (A) and change in fasting glycemia (B) (expressed as Δ).

ment, the values of sICAM-1 were slightly but not significantly lower, ranging from 179 to 250 ng/ml with a median of 210 ng/ml.

Metabolic changes

Biological parameters in NIDDM patients on day 0 and after a 14-day CSII treatment and in the control group are summarized in Table 2. There was no change in body weight after CSII treatment. Glycemic control was significantly improved at day 15 compared with day 0. There was no significant difference between day 0 and day 15 for plasma insulin and C-peptide. As for lipid changes, there were significant reductions in total cholesterol (5.6 ± 0.3 vs. 4.6 ± 0.3 mmol/l, $P < 0.0001$), triglycerides (1.9 ± 0.1 vs. 1.1 ± 0.1 mmol/l, $P = 0.006$), LDL cholesterol (4.1 ± 0.3 vs. 3.3 ± 0.3 mmol/l, $P = 0.0001$), apo A₁ (1.5 ± 0.1 vs. 1.2 ± 0.1 g/l, $P = 0.0002$), and apo B (1.2 ± 0.1 vs. 1.0 ± 0.1 g/l, $P < 0.0001$), without significant changes in HDL cholesterol or Lp(AI).

Correlation between adhesion glycoproteins and blood parameters

In the blood samples obtained at day 0, sE-

selectin and sVCAM-1 levels did not correlate significantly with fasting values of glycemia (respectively, $r = 0.12$, $P = 0.65$; $r = -0.03$, $P = 0.91$), insulin (respectively, $r = 0.4$, $P = 0.12$; $r = 0.04$, $P = 0.89$), HbA_{1c} (respectively, $r = -0.04$, $P = 0.88$; $r = 0.004$, $P = 0.99$), fructosamine (respectively, $r = 0.2$, $P = 0.40$; $r = 0.1$, $P = 0.56$), or total cholesterol (respectively, $r = -0.47$, $P = 0.07$; $r = -0.17$, $P = 0.54$). Interestingly, at day 15 but not at day 0, sE-selectin correlated negatively with plasma fasting C-peptide ($r = -0.56$, $P = 0.03$).

The fall in sE-selectin levels between day 0 and day 15 was correlated negatively with the change in apo A₁ ($r = -0.49$, $P =$

0.05) (Fig. 2A) and positively with the change in fasting glycemia ($r = 0.58$, $P = 0.02$) (Fig. 2B).

To estimate the metabolic factor(s) that may be associated with the fall of sE-selectin between day 0 and day 15, logistic regression analysis was applied. For this purpose, we coded sE-selectin levels using a variable threshold inside the interval (60–90 ng/ml), including the two medians related to day 0 and day 15, respectively, thus creating a series of new dichotomous qualitative variables coded yes or no as inferior to a chosen value for the threshold. Then a multivariate logistic regression was performed using sE-selectin levels, on day 0 and on day 15, as the dependent variable and the series of new dichotomous variables as independent variables. The best fit was obtained for the single threshold value of 85 ng/ml with an odds ratio (OR) equal to 4.30 (95% CI 1.92–9.80). Assuming this cutoff, a logistic model was applied using sE-selectin as the dependent variable and potential explanatory variables, including apo A₁, LDL cholesterol, triglycerides, C-peptide, and fasting glycemia, as independent variables. Our model clearly indicated that LDL cholesterol and fasting glycemia were the most strongly associated with the fall in sE-selectin ($P = 0.02$ and $P = 0.03$, respectively) (Table 3).

CONCLUSIONS— The most important observation of the present study is the significant fall in sE-selectin levels after a 14-day intensive insulin treatment together with an improvement of the glycemic control and a decrease of total cholesterol and triglycerides. In addition, under these conditions, sVCAM-1 values were also lowered; sICAM-1 levels did not significantly differ from those observed in the healthy subjects. Note that in all of our patients in the present study, normal serum CRP and orosomucoid levels were observed, ruling out the possibility that the expression of adhesion glycoproteins was induced by acute or chronic inflammation. Our results

Table 3—Multivariate logistic regression, final multivariate model, when entering sE-selectin as the dependent variable (cutoff = 85 ng/ml) and LDL cholesterol and fasting glycemia as independent variables

Variable	Wald	P (Wald)	Adjusted OR (95% CI)	Crude OR (95% CI)
LDL cholesterol	5.48	0.02	4.07 (2.23–7.40)	1.84 (1.26–2.70)
Fasting glycemia	4.65	0.03	0.67 (0.55–0.81)	0.81 (0.72–0.92)
Constant	1.29	0.26	—	—

are in accordance with those of Steiner et al. (16), which showed that sVCAM-1 and sE-selectin levels were significantly elevated in NIDDM patients with poor glycemic control, before insulin treatment.

However, we did not observe, at baseline, any correlation between the elevated levels of adhesion molecules and the different parameters used to evaluate glycemic control (fasting glycemia, HbA_{1c}, and fructosamine). The positive correlation between the change in fasting blood glucose and sE-selectin levels, after a 14-day insulin treatment, is consistent with a direct role played by high blood glucose concentrations, but it does not exclude an additive indirect effect exerted by AGEs on serum glycoprotein disturbances (12).

Regarding an improvement of insulin secretion, we have previously shown that a 14-day CSII treatment improves insulin secretion, since the glucagon-induced plasma C-peptide increase was similar to that before CSII, whereas glycemia had markedly decreased (18,20). In the present study, after CSII, sE-selectin levels were found to be significantly and negatively correlated with C-peptide, which suggests that in poorly controlled NIDDM patients, the lower the insulin secretion, the higher the sE-selectin levels. This also suggests that an improvement in insulin secretion may be involved in the significant fall and return to normal of sE-selectin and near-to-normal return of sVCAM-1. However, this does not exclude a proper effect of insulin, in so far as an activating effect of insulin on nitric oxide synthase has been reported (21,22).

Insulin treatment may also have acted through changes in lipid parameters. Indeed, we observed a negative correlation between the changes in sE-selectin and apo A₁. The multivariate analysis including apo A₁, but also LDL cholesterol, triglycerides, C-peptide, and fasting glycemia as independent variables, showed a significant association between the fall in sE-selectin and LDL cholesterol and fasting glycemia. These observations, associated with data that dyslipidemia is also characterized by increased sE-selectin levels (23), suggest a possible role of LDL cholesterol decrease in the fall of E-selectin during insulin treatment.

Along this line, additional metabolic aberrations, such as oxidation of LDL cholesterol, as suggested by Cominacini et al. (24), may add to the appearance of elevated circulating adhesion molecules in poorly controlled NIDDM patients.

E-selectin is expressed on activated endothelium, whereas VCAM-1 is expressed mostly on these cells but also on various circulating blood cells. Therefore, high sE-selectin levels can be associated with endothelial dysfunction that, in fact, precedes the development of atherosclerotic lesions in diabetic patients. In addition, the significant increase in sVCAM-1 levels observed here in NIDDM patients with poor glycemic control and the return to normal of E-selectin levels associated with a decrease of VCAM-1 levels under intensive insulin treatment is in accordance with not only endothelial dysfunction but also abnormal adhesion events between blood cells and endothelium and their improvement under an adequate therapy.

In conclusion, in the present study we observed significant increases in sE-selectin and sVCAM-1 levels and a fall in both of these levels (but to a lesser extent for sVCAM-1) after a 14-day intensive insulin treatment in poorly controlled NIDDM patients, thus confirming our previous preliminary assessments (25). These results may be related to endothelial cell dysfunction and abnormal adhesion events between blood cells and the endothelium that are improved under insulin treatment in poorly controlled NIDDM patients. Our results suggest that assaying sE-selectin and sVCAM-1 makes it possible to detect endothelium activation and to follow its reversal with euglycemia and appropriate insulin treatment. Whether these elevated levels of circulating adhesion glycoproteins suggest abnormal adhesion events between blood cells and the endothelium has to be determined with larger studies including patients with silent or patent ischemic disorders.

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