Effects of Heparin Treatment on Hemostatic Abnormalities in Obese Non–Insulin-Dependent Diabetic Patients

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This study was conducted to identify the mechanisms responsible for coagulative and fibrinolytic alterations and to study the effects of a short-term treatment with low-dose heparin on hemostatic abnormalities in obese non–insulin-dependent diabetes mellitus (NIDDM) patients. Four groups of age- and sex-matched patients were studied: (1) lean nondiabetic subjects (n = 30) with a body mass index (BMI) less than 25 kg/m^2 (lean control subjects), (2) obese nondiabetic subjects (n = 30) with a BMI greater than 30 kg/m^2 (obese control subjects), (3) lean NIDDM patients (n = 30), and (4) obese NIDDM patients (n = 30). All subjects were tested on the following parameters: fibrinogen, factor VII, prothrombin fragment 1 + 2 (F1 + 2), thrombin–antithrombin III complexes (TAT), tissue plasminogen activator (t-PA) antigen (Ag) before and after venous occlusion (VO), and plasminogen activator inhibitor type-1 (PAI-1) activity pre- and post-VO. In addition, all these parameters were evaluated in obese NIDDM patients after 10 days of treatment with a single dose of 12,500-U/d subcutaneous calcium heparin and after a 10-day washout period. At baseline, obese nondiabetic subjects, lean NIDDM patients, and especially obese NIDDM patients displayed significantly ($P < .01$) higher levels of fibrinogen, factor VII, F1 + 2, TAT, t-PA(Ag) pre-VO, and PAI-1 pre- and post-VO and significantly ($P < .01$) lower levels of t-PA(Ag) post-VO. In obese NIDDM patients treated with heparin fibrinogen, factor VII, F1 + 2, TAT, t-PA(Ag) pre-VO, and PAI-1 pre- and post-VO levels significantly ($P < .01$) decreased and t-PA(Ag) post-VO levels significantly ($P < .01$) increased at the end of treatment. Our findings demonstrate in obese nondiabetic subjects, lean NIDDM patients, and especially obese NIDDM patients the hemostatic abnormalities contributing to an enhanced risk of thrombotic complications. We conclude that in obese NIDDM patients, short-term treatment with heparin may reduce this thrombophilic state and have a potential benefit in the progression of diabetic microvascular and macrovascular disease and needs further investigation.

IT IS WELL KNOWN that the mortality rate in patients with non–insulin-dependent diabetes mellitus (NIDDM) is twice that in normal subjects, and that accelerated atherosclerosis and atherosclerosis-related complications represent the leading cause of death in patients with diabetes mellitus.[1-2] This observation is in agreement with the widely accepted concept that hyperglycemia and diabetes-related lipid metabolism abnormalities, together with nonenzymatic glycosylation of proteins (including lipoproteins), may affect endothelial cell function that have been shown to be crucial in modulating the coagulation/fibrinolysis balance.[3-5]

Although many coagulative and fibrinolytic abnormalities in diabetes mellitus have been described, the existence of a hypercoagulable state and the contribution of abnormalities of the coagulative and fibrinolytic mechanisms to the pathogenesis of vascular damage in diabetes mellitus are controversial.[6-8]

Moreover, in NIDDM patients, other disease states (such as obesity, dyslipidemia, and hypertension) are frequently present, which could independently interfere with the coagulation and fibrinolytic system.[9] Obesity, which predisposes to insulin resistance and hyperinsulism, may play a key role in the pathogenesis of atherosclerotic complications.[10-12]

This investigation was conducted to identify mechanisms responsible for coagulative and fibrinolytic alterations and to study the effects of short-term treatment with low-dose heparin on hemostatic abnormalities in obese NIDDM patients.

SUBJECTS AND METHODS

Four groups of age- and sex-matched subjects were studied: (1) lean nondiabetic subjects (n = 30) with a body mass index (BMI) less than 25 kg/m^2 (lean control subjects), (2) obese nondiabetic subjects (n = 30) with a BMI greater than 30 kg/m^2 (obese control subjects), (3) lean NIDDM patients (n = 30), and (4) obese NIDDM patients (n = 30).

Patients with NIDDM, recruited in accordance with World Health Organization criteria,[13] were treated with oral hypoglycemic agents and were in a satisfactory state of metabolic control as shown by glycosylated hemoglobin levels (from 5.8% to 8.2%). Obesity was definited as a BMI greater than 30 kg/m^2 in accordance with Garrow criteria.[14] None of the patients had a personal history or clinical evidence of myocardial infarction or coronary heart disease. Hypertensive patients were not admitted to the study (exclusion criteria: use of antihypertensive drugs and diastolic blood pressure greater than 95 mm Hg and/or systolic blood pressure >160 mm Hg). Patients with acute or chronic infections (assessed by increased C-reactive protein and erythrocyte sedimentation rate), impaired hepatic function (associated with synthetic dysfunction), and renal disease (definited as serum creatinine >2.0 mg/dL) were also excluded. All patients were tested for diabetic lesions by fundoscopy, electrocardiography, and arterial Doppler measurements. All subjects provided informed consent before the investigation and were asked not to take any drugs at least 20 days before the study, except for oral hypoglycemic agents in NIDDM patients. None of the diabetic patients had ever been treated with insulin. All diabetic subjects were normoalbuminuric (albumin excretion rate, 4.0 ± 1.5 μg/min). On the day of each study, patients who were being treated with oral hypoglycemic agents delayed taking the morning dose until after all blood samples had been obtained. Further clinical characteristics of the patients and control subjects are listed in Table 1.

Blood collection was performed only between 8 and 9 AM and after an

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Table 1. Subject Characteristics

Characteristic	Nondiabetic		Diabetic	
	Lean (n = 30)	Obese (n = 30)	Lean (n = 30)	Obese (n = 30)
Age (yr)	47.8 ± 3.1	49.2 ± 3.4	48.6 ± 2.8	50.2 ± 3.6
Sex (M/F)	12/18	13/17	12/18	13/17
BMI (kg/m²)	23.5 ± 0.8	36.4 ± 2.8*	24.0 ± 0.3	38.1 ± 3.2*
WHR	0.86 ± 0.05	0.89 ± 0.04	0.88 ± 0.04	0.90 ± 0.05
Current smokers (n)	12	11	13	12
Duration of diabetes (yr)			7.5 ± 2.5	8.5 ± 3.0

*$P < .01$ *v* lean control subjects.

8-hour abstinence from smoking and physical exercise. Blood was drawn from an antecubital vein after overnight fasting using a 1.2-mm siliconized needle with or without minimal stasis.

Using conventional enzymatic methods (Boehringer Mannheim, Milan, Italy), we determined levels of serum triglycerides (glycerol phosphate oxidase), total cholesterol (cholesterol oxidase), and high-density lipoprotein (HDL) cholesterol (after precipitation by dextran-magnesium chloride) and blood glucose levels (glucose oxidase). Apolipoproteins A1 and B were determined by radial immunodiffusion (Behring plates; Behring Institute, Scoppito, Italy), plasma insulin by a radioimmunoassay (Sorin Biomedica, Saluggia, Italy), and lipoprotein(a) [Lp(a)] by an enzyme-linked immunosorbent assay (ELISA) (IMMUNO, Pisa, Italy).

Blood samples for coagulative and fibrinolytic variables were drawn, after discarding the first 2 mL, into polypropylene tubes containing a one-tenth final volume of 3.8% sodium citrate. Blood was kept on crushed ice until centrifugation (2,500 × *g* at 4°C for 15 minutes), and plasma was stored in small aliquots at −70°C until use. At the same time, a venous occlusion (VO) test was performed in all subjects. A sphygmomanometer cuff was applied to the contralateral arm and inflated midway between systolic and diastolic pressure for 10 minutes. A further blood sample was obtained before deflating the cuff from the occluded arm and separated as before.

The following parameters were determined: fibrinogen by radial immunodiffusion (Behring), factor VII by chromogenic substrate assay with reagents obtained from Behring (using an automated device, Behring Chromo Time System), prothrombin fragment 1 + 2 (F1 + 2) (ELISA; Behring), thrombin–antithrombin III complexes (TAT) (ELISA; Behring), tissue plasminogen activator (t-PA) antigen (Ag) pre- and post-VO (ELISA; Innogenetics, Antwerp, Belgium), and plasminogen activator inhibitor type-1 (PAI-1) pre- and post-VO (Behring Chromo Time System).

In addition, obese diabetic patients (group 4) were treated with a commercial calcium heparin preparation (Calciparina; Italfarmaco, Milan, Italy) at a dose of 12,500 U/d in 0.5 mL distilled water subcutaneously for 10 days. Calcium heparin was administered at 8 AM in a single dose. All the above-mentioned parameters were evaluated after 10 days of treatment and after 10 days of a washout period.

Analysis was performed in duplicate following the manufacturer's instructions and, in one series for each participant, within 6 months after sampling. All values are expressed as the mean ± SD. Between-group differences were tested by ANOVA and Kruskal-Wallis nonparametric tests. Comparisons between two groups were performed using Student's *t* tests. Data from the four groups at baseline were pooled, and correlations of the hemostatic variables with glucose and insulin levels and glycosylated hemoglobin were examined with the use of Pearson coefficients.

RESULTS

Baseline characteristics of the four subject groups are shown in Table 1. No significant differences were noted in the distribution of age, sex, waist to hip ratio (WHR), smoking status, and duration of diabetes between groups. As expected, BMI was significantly ($P < .01$) higher in obese nondiabetic subjects and in obese diabetic patients than in lean control subjects.

Triglycerides, apolipoprotein B, and plasma insulin were significantly ($P < .01$) higher and HDL cholestrol and apolipoprotein A1 were significantly ($P < .01$) lower in obese nondiabetic subjects and in both lean and obese NIDDM patients than in lean control subjects (Table 2). Blood glucose and Lp(a) were significantly ($P < .01$) higher in lean and obese diabetic patients than in lean control subjects, and total cholesterol was significantly ($P < .01$) higher in obese NIDDM patients than in lean control subjects. Moreover, triglycerides, apolipoprotein B, Lp(a), and plasma insulin were significantly ($P < .01$) higher and HDL cholesterol was significantly ($P < .01$) lower in obese NIDDM patients than in lean NIDDM patients.

Fibrinogen, factor VII, F1 + 2, TAT, t-PA(Ag) pre-VO, and PAI-1 pre- and post-VO were significantly ($P < .01$) higher and t-PA(Ag) post-VO was significantly ($P < .01$) lower in obese nondiabetic subjects and in both lean and obese NIDDM patients than in lean control subjects (Table 3). Moreover, fibrinogen, F1 + 2, t-PA(Ag) pre-VO, and PAI-1 pre- and post-VO were significantly ($P < .01$) higher in obese NIDDM patients than in lean NIDDM patients.

In obese diabetic patients treated with heparin (Table 4), fibrinogen, factor VII, F1 + 2, TAT, t-PAI pre-VO, and PAI-1 pre- and post-VO were significantly ($P < .01$) decreased and t-PA post-VO were significantly ($P < .01$) increased at the end

Table 2. Metabolic Parameters

Parameter	Nondiabetic		Diabetic	
	Lean (n = 30)	Obese (n = 30)	Lean (n = 30)	Obese (n = 30)
Blood glucose (mg/dL)	89.1 ± 3.3	92.3 ± 4.5	123.4 ± 5.6*	128.0 ± 6.2*
Total cholesterol (mg/dL)	198.5 ± 19.9	220.6 ± 46.8	222.3 ± 30.5	245.3 ± 24.6*
Triglycerides (mg/dL)	128.7 ± 22.4	213.2 ± 21.7*	187.5 ± 28.9*	248.9 ± 38.6*†
HDL cholesterol (mg/dL)	42.5 ± 2.4	31.7 ± 4.1*	34.4 ± 3.8*	30.5 ± 4.6*†
Apolipoprotein A1 (mg/dL)	139.2 ± 12.5	117.3 ± 13.6*	118.8 ± 10.6*	110.4 ± 11.9*
Apolipoprotein B (mg/dL)	106.9 ± 13.8	163.5 ± 22.8*	159.5 ± 21.5*	180.3 ± 12.8*†
Lp(a) (mg/dL)	7.0 ± 5.9	12.9 ± 11.5	19.3 ± 10.4*	36.5 ± 18.8*†
Plasma insulin (mU/L)	4.8 ± 1.1	12.3 ± 2.7*	13.6 ± 3.8*	19.2 ± 2.9*†

*$P < .01$ *v* lean control subjects.

†$P < .01$ *v* lean diabetic patients.

Table 3. Hemostatic Parameters

Parameter	Nondiabetic		Diabetic	
	Lean (n = 30)	Obese (n = 30)	Lean (n = 30)	Obese (n = 30)
Fibrinogen (mg/dL)	316.7 ± 38.3	388.2 ± 46.8*	406.3 ± 35.2*	480.2 ± 66.2*†
Factor VII (%)	81.5 ± 12.3	118.7 ± 21.9*	128.2 ± 16.7*	135.9 ± 25.9*
F1 + 2 (nmol/L)	0.85 ± 0.24	2.02 ± 0.31*	1.82 ± 0.26*	2.29 ± 0.24*†
TAT (mg/L)	2.51 ± 1.24	4.93 ± 2.37*	5.78 ± 2.99*	7.55 ± 3.68*
t-PA (Ag) (ng/mL)				
Pre-VO	4.4 ± 0.8	7.9 ± 2.5*	7.7 ± 2.6*	10.6 ± 2.4*†
Post-VO	25.7 ± 4.4	13.7 ± 2.6*	14.1 ± 3.4*	12.8 ± 3.5*
PAI-1 (U/mL)				
Pre-VO	1.6 ± 0.5	6.9 ± 2.3*	6.5 ± 1.9*	9.7 ± 2.3*†
Post-VO	1.3 ± 0.4	8.5 ± 2.2*	7.9 ± 2.5*	11.8 ± 3.1*†

*$P < .01$ *v* lean control subjects.
†$P < .01$ *v* lean diabetic patients.

of treatment. All of these parameters returned to baseline after 10 days of a washout period.

At baseline, neither glucose nor glycosylated hemoglobin levels correlated with the coagulative and fibrinolytic variables. Instead, insulin levels were significantly correlated with fibrinogen ($r = .48$, $P < .01$), factor VII ($r = .43$, $P < .01$), F1 + 2 ($r = .45$, $P < .01$), TAT ($r = .37$, $P < .05$), PAI-1 pre- and post-VO ($r = .55$, $P < .01$ and $r = .52$, $P < .01$, respectively), and t-PA pre-VO ($r = .38$, $P < .05$). A significant negative correlation was also found between insulin levels and t-PA post-VO ($r = -.44$, $P < .01$).

DISCUSSION

Our results indicate that obese nondiabetic subjects and lean and obese NIDDM patients in good metabolic control and without microvascular and macrovascular disease exhibit an activation of the coagulation system and a decreased fibrinolytic activity during basal conditions and after VO. These hemostatic abnormalities, which may play a key role in the pathogenesis of atherosclerotic complications, are more marked in obese NIDDM patients. In particular, in obese NIDDM patients we found significantly higher fibrinogen, factor VII, F1 + 2, and TAT levels, which are an expression of an elevated turnover of the coagulation pathway and may be involved in the pathogenesis of atherosclerotic vascular disease.[15,16] Especially F1 + 2 and TAT, markers of thrombin generation, today are considered good tools to reveal an existing thrombophilia, and have been reported in the majority of patients with ischemic heart disease.[5,7,8]

Table 4. Hemostatic Pattern in Obese NIDDM Subjects (n = 30) at Baseline, After 10 Days of Treatment With Heparin, and After 10-Day Washout Period

Parameter	Baseline	+10 Days	+20 Days
Fibrinogen (mg/dL)	480.2 ± 66.2	363.7 ± 76.6*	488.5 ± 76.4
Factor VII (%)	135.9 ± 25.9	116.3 ± 23.7*	132.2 ± 26.8
F1 + 2 (nmol/L)	2.29 ± 0.24	1.43 ± 0.44*	2.32 ± 0.33
TAT (μg/L)	7.55 ± 3.68	2.69 ± 3.48*	8.23 ± 4.13
t-PA(Ag) (ng/ml)			
Pre-VO	10.6 ± 2.4	6.6 ± 3.4*	9.9 ± 3.7
Post-VO	12.8 ± 3.5	22.8 ± 3.9*	13.5 ± 4.5
PAI (U/mL)			
Pre-VO	9.7 ± 2.3	5.9 ± 2.6*	8.8 ± 4.1
Post-VO	11.8 ± 3.1	5.5 ± 3.1*	11.3 ± 3.5

*$P < .01$ *v* baseline.

As regards fibrinolytic variables, obese NIDDM patients showed significantly higher baseline levels of PAI-1 and t-PA(Ag) and a deficient release of t-PA(Ag) post-VO. Moreover, we found significantly higher levels of Lp(a) in lean and obese NIDDM patients, and data are accumulating to demonstrate that increased Lp(a) levels inhibit plasminogen activation.[17] The finding of increased baseline levels of t-PA(Ag) in the presence of reduced fibrinolytic activity can be explained on the basis of the occurrence of inactive t-PA/PAI-1 complexes in blood resulting in reduced free t-PA levels.[6,18]

In the present study, the coagulation and fibrinolytic abnormalities seem to be independent of metabolic control, as reflected by glycosylated hemoglobin levels. On the other hand, our data support the hypothesis of a key role of hyperinsulinemia in promoting the activation of coagulation and depressed fibrinolytic activity in obese nondiabetic subjects and in lean and obese NIDDM patients in good metabolic control. In fact, neither glucose nor glycosylated hemoglobin levels correlated with the hemostatic variables. Instead, insulin levels were significantly correlated with fibrinogen ($r = .48$), factor VII ($r = .43$), F1 + 2 ($r = .45$), TAT ($r = .37$), PAI-1 pre- and post-VO ($r = .55$ and $r = .52$, $P < .01$, respectively), and t-PA pre-VO ($r = .38$). A significant negative correlation was also found between insulin levels and t-PA post-VO ($r = -.44$).

In addition, our results suggest that a VO test can demonstrate an impaired fibrinolytic potential related to abnormalities of endothelial cell function. Several studies support the hypothesis that abnormalities in lipid and carbohydrate metabolism contribute to the development of vascular damage, and that high concentrations of circulating immunoreactive insulin predispose to thrombosis and to impaired fibrinolysis.[6,7] More recently, PAI-1 activity has been proposed as a marker of hypofibrinolysis and a predictor of coronary atherosclerosis, and a significant correlation between PAI-1 and plasma insulin was also reported.[19-21] Others have hypothesized that impaired fibrinolysis may potentially accelerate atherosclerosis and be an important link between hyperinsulinemia and atherosclerosis in NIDDM and perhaps in other conditions.[7,11]

It is known that obese NIDDM patients exhibit hyperinsulin-

emia and may develop insulin resistance. An association between hyperinsulinemia and atherosclerotic vascular complications in nondiabetic patients was also observed.[22] Moreover, it has been shown that obese nondiabetic subjects exhibit hyperinsulinemia, and high PAI-1 levels were reported in both diabetics and nondiabetics.[10,11,23] Apart from insulin, PAI-1 levels also seem to be influenced by other metabolic risk factors like triglyceride levels, which are significantly higher in obese nondiabetic subjects and in NIDDM patients of this study.[12,24,25] The increase in factor VII in hyperlipidemic states could also be linked to the triglyceride content of lipoproteins.[26]

Recent studies have reported that obesity is a potential cardiovascular risk factor that becomes apparent only after long periods through its association with coexisting risk factors. Obesity, particularly with abdominal body fat distribution, is also a component of the so-called "polymetabolic syndrome" or "syndrome X," which is closely related to hyperlipidemia, hypertension, and both impaired glucose tolerance and NIDDM.[9,27-29] Moreover, positive correlations between factor VII and BMI and between fibrinogen and BMI and a negative correlation between fibrinolytic activity and BMI have been reported.[12,30-31]

In concert with these notions, we found that especially obese NIDDM patients have an activation of the coagulation system and an impaired fibrinolytic activity, which could be an expression of vascular damage. On the other hand, abnormalities of lipid and carbohydrate metabolism associated with obesity may cause endothelial damage and have been implicated in hemostatic alterations.[32-34] The link between endothelial dysfunction, lipoprotein abnormalities, or both and the existence of a hypercoagulable state may be key in the pathogenesis of atherosclerotic vascular complications in obesity and in NIDDM, and are being investigated further.

Additional information with regard to the relationship between endothelial dysfunction and hemostatic alterations may be provided by data obtained from short-term treatment with low-dose heparin in obese diabetic patients. It is known that heparin at a low dose is a safe and effective drug for reducing increased thrombin generation without interfering with prothrombin time and partial thromboplastin time in patients at high risk for thrombotic complications.[35] In fact, it protects against thrombosis by binding to endothelial cells and thereby enhancing endothelial mechanisms that inactivate thrombin and activated factor X.[35]

Our data obtained as a result of short-term treatment with low-dose heparin in obese NIDDM patients are in agreement with the evidence of a decrease of thrombin generation after heparin administration in normal subjects in whom a hyperglycemic state has been artificially produced.[36] Moreover, the simultaneous decrease of fibrinogen, factor VII, F1 + 2, TAT, t-PA, and PAI-1 levels after heparin treatment gives support to the hypothesis of the existence of a positive feedback between thrombus formation, fibrinolysis, and fibrinogen production.[37]

Many research studies report that hyperglycemia increases fibrinogen turnover and that metabolic control may influence fibrinogen levels.[34,38] However, it has been recently shown that hemostatic abnormalities contributing to an enhanced risk of thrombotic complications persist despite glycemic improvement by insulin therapy in NIDDM.[33] In agreement with this observation, in the present study hemostatic abnormalities seem to be independent of metabolic control by hypoglycemic agents.

Therefore, we suggest a short-term treatment with heparin at low dose in patients at high risk of thrombotic complications, such as diabetics hospitalized for acute surgery or immobilization. This therapeutic approach may reduce the thrombophilic state and, by intervening in endothelial atherogenic mechanisms, have a potential beneficial effect on endothelial dysfunction and on the progression of diabetic microvascular and macrovascular disease. However, because of the uncontrolled nature of short-term treatment with heparin, our preliminary observations in obese NIDDM patients require confirmation in a placebo-controlled long-term study.

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