Hyperfibrinogenemia

An important risk factor for vascular complications in diabetes

OM P. GANDA, MD
CHARLES F. ARKIN, MD

OBJECTIVE — To evaluate the determinants of elevated fibrinogen levels and the impact of hyperfibrinogenemia on vascular complications in diabetes.

RESEARCH DESIGN AND METHODS — Plasma fibrinogen, glucose, HbA_1, and lipids were measured in 116 ambulatory type I and type II diabetic patients with (n = 59) or without (n = 57) clinical evidence of micro- or macrovascular complications. In 56 of these patients, factor VII activity and CRP also were measured. Univariate and multivariate data analyses were conducted.

RESULTS — Overall mean ± SE fibrinogen levels in patients (339 ± 7.3 mg/dl) were elevated markedly compared with control subjects (248 ± 9.1 mg/dl). Fibrinogen levels were elevated disproportionately in patients with type II diabetes ($P < 0.0001$), hypertension ($P = 0.0001$), obesity ($P < 0.0001$), and vascular complications ($P < 0.0001$). Fibrinogen was correlated significantly with age ($P < 0.001$), cholesterol ($P = 0.002$), CRP ($P < 0.001$), and factor VII activity ($P = 0.032$), but not with plasma glucose, triglycerides, HDL cholesterol, or disease duration. Stepwise multiple regression analyses revealed that type II diabetes and presence of vascular complications were major determinants of fibrinogen. For vascular complications, fibrinogen emerged as one of only three independent predictors, the other two being diabetes duration and hypertension.

CONCLUSIONS — Fibrinogen frequently is elevated in diabetes and is an independent predictor of vascular complications.

Prospective, epidemiological studies from Goteborg, Sweden (1), London, UK (2), and Framingham, MA (3), have identified elevated fibrinogen as a risk factor for cardiovascular disease. This relationship persisted in multivariate analyses, taking into account traditional risk factors, which included smoking, cholesterol, and hypertension. In the Northwick Park Heart Study (2), hemostatic factors, i.e., fibrinogen and factor VII coagulant activity, were stronger predictors for ischemic heart disease than was cholesterol. In another long-term prospective study (4), fibrinogen levels were a strong and independent predictor of acute heart attacks after adjusting for systolic blood pressure and cholesterol. Along with evidence for a role of fibrin deposition in the development of atherosclerotic lesions (5,6), such observations provide support for the theory of thrombogenesis in the evolution of atherosclerosis (7).

Abundant evidence has accumulated to suggest that atherosclerosis is accelerated in both type I (8,9) and type II (10,11) diabetes. Traditional risk factors (hyperlipidemia, hypertension, smoking, age, obesity) do not account fully for the increased prevalence and severity of vascular disease in diabetes (12). It has been proposed that a hypercoagulable state in diabetes may contribute at least in part (13). Of the various hematological factors, elevated fibrinogen as a risk factor in diabetes has received little attention. A few cross-sectional studies have indicated a state of hyperfibrinogenemia in diabetes compared with nondiabetic control subjects (14–18), particularly in those with preexisting micro- or macrovascular complications. However, these studies were not controlled for confounding variables.

In this study, we examined the relationship of plasma fibrinogen and other clinical variables to vascular complications in 116 patients with a wide range of diabetes duration, severity, and glycemic control.

RESEARCH DESIGN AND METHODS

— The study population included 116 diabetic outpatients presenting for an office visit to O.P.G. over a period of several weeks. Pertinent information, including the presence or ab-

FROM THE JOSLIN DIABETES CENTER AND THE DEPARTMENTS OF MEDICINE AND PATHOLOGY, NEW ENGLAND DEACONESS HOSPITAL, AND THE HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO OM P. GANDA, MD, JOSLIN DIABETES CENTER, ONE JOSLIN PLACE, BOSTON, MA 02215.

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TYPE I DIABETES, INSULIN-DEPENDENT DIABETES MELLITUS; TYPE II DIABETES, NON-INSULIN-DEPENDENT DIABETES MELLITUS; CRP, C-REACTIVE PROTEIN; OHA, ORAL HYPOGLYCEMIC AGENT; HDL, HIGH-DENSITY LIPOPROTEIN.

Table 1—*Study population*

	N (M/W)	AGE (YR) (RANGE)	DURATION OF DIABETES (YR) (RANGE)	VASCULAR COMPLICATIONS			TREATMENT		
				NONE	MICRO	MACRO	DIET	OHA	INSULIN
CONTROL SUBJECTS	30 (18/12)	46.4 ± 2.55 (23–71)	—	—	—	—	—	—	—
PATIENTS (ALL)	116 (55/61)	56.6 ± 1.44 (22–82)	12.2 ± 0.90 (1–60)	57	32	41	4	30	82
TYPE I	36 (19/17)	41.3 ± 2.3 (22–75)	15.2 ± 2.1 (1–60)	22	11	6	0	0	36
TYPE II	80 (36/44)	63.5 ± 1.2 (36–82)	10.8 ± 0.9 (1–35)	35	21	35	4	30	46

Values for age and duration of diabetes are means ± SE.
Three type I and 11 type II patients had both micro- and macrovascular complications.

sence of clinical evidence of vascular complications in each patient, was recorded by the same researcher. The means (and ranges) of age and diabetes duration, and the sex, treatment modalities, and status of vascular complications are presented in Table 1. Microvascular complications included presence of background or proliferative retinopathy and/or nephropathy. Retinopathy was classified based on the funduscopic and fluorescein angiographic assessment at the Beetham Eye Unit at our institution. Nephropathy was defined by the presence of overt, dipstick-positive proteinuria in the absence of infection or other discernible cause; most patients had also additional evidence of diabetic nephropathy. Macrovascular disease also was defined by standard clinical criteria, including a detailed checklist of history and physical examination, routine and stress electrocardiography, and noninvasive and/or invasive peripheral vascular studies in most patients. Of the 80 patients with type II diabetes, 35 had various combinations of coronary artery disease (n = 22), peripheral vascular disease (n = 13), defined by history of lower extremity vascular bypass procedure (n = 6) or evidence of absent pulsations, and/or amputation (n = 7); and cerebrovascular disease, as indicated by history of stroke, transient ischemic attacks, or carotid bruit (n = 8). Twenty-one patients, including 11 with macrovascular disease, had microvascular disease. Of the 36 type I diabetes patients, 14 had evidence of vascular complications, 11 had microvascular disease, and 6 had macrovascular disease. Altogether, of 116 patients, 57 patients had no evidence of vascular complications, and 59 had micro- and/or macrovascular complications. Only 12 patients were smokers. Obesity, defined as ≥120% of ideal body weight, was prevalent in type II patients (63 of 80 [79%]), whereas only 3 type I patients (8%) were obese. For comparison, 30 healthy nondiabetic laboratory technologists or blood-bank donors of similar age range (23–71 yr) served as control subjects.

Procedures

Random (fasting or nonfasting) blood samples were obtained for glucose, HbA_1, lipids (total cholesterol, triglycerides, HDL cholesterol), and fibrinogen determinations. Plasma glucose and lipids were determined by routine autoanalyzer methodology with enzymatic techniques (19). HbA_1 was determined by an electrophoretic method (20). For plasma fibrinogen assay, the Dade thrombin clotting time methodology was used (21). In 56 of the patients (25 with and 31 without vascular complications), plasma factor VII activity (22) and CRP (23) also were determined.

Statistics

Unpaired Student's t tests were conducted to determine the significance of observed differences between the means of continuous and discontinuous variables. Nonparametric analyses (Kruskall-Wallis test and Wilcoxon's signed-rank test) were applied for the nonnormally distributed differences in patients and control subjects. Results are presented as means ± SE. Simple and multiple regression analyses using stepwise regressions were performed with Minitab Software Release 7.2.

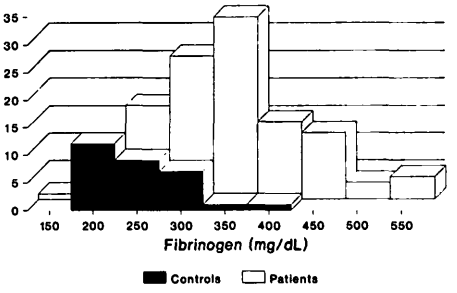

Figure 1—*Distributions of fibrinogen concentrations in control subjects (n = 30) and diabetes patients (n = 116). $P < 0.0001$. See RESULTS for details of statistical analyses.*

Table 2—*Distribution of fibrinogen levels by discontinuous variables in all patients*

	N	Fibrinogen levels* (mg/dl)	P
Complications			
No (group A)	57	307 ± 9.3	
Yes (group B)	59	369 ± 9.8	<0.0001
Hypertension			
No	67	314 ± 9.1	0.0001
Yes	49	372 ± 10.0	
Obesity			
No	50	304 ± 10.0	
Yes	66	365 ± 9.1	<0.0001
Sex			
Men	55	339 ± 12.0	0.97
Women	61	338 ± 9.0	
Smoking			
No	104	339 ± 7.7	0.93
Yes	12	337 ± 25.0	
Type diabetes			
II	80	362 ± 8.5	<0.0001
I	36	288 ± 10.0	

*Values are means ± SE. Fibrinogen levels in 30 control subjects was 248 ± 9.1 compared with 339 ± 7.3 mg/dl in 116 diabetic patients ($P < 0.0001$).

RESULTS

Fibrinogen levels and clinical variables

In initial comparisons, no differences were observed between patients with macrovascular and microvascular complications. Some patients (3 type I and 11 type II diabetic patients) had both types of complications, on the clinical basis described above. Therefore, results of all patients with vascular complications (micro- and/or macrovascular) were grouped together as group B and compared with all patients without vascular complications (group A).

Figure 1 presents the overall distribution of fibrinogen levels across the patient population, in juxtaposition to that in control subjects. The mean fibrinogen levels in patients as distributed by major variables, i.e., complications, hypertension, obesity, sex, smoking status, and type of diabetes, are shown in Table 2.. Mean fibrinogen levels were elevated markedly in all of the diabetic patients compared with control subjects. These differences were highly significant as determined by unpaired Student's *t* tests ($P < 0.0001$) and by nonparametric tests, including the Kruskall-Wallis test and the Wilcoxon's signed-rank test ($P < 0.0005$).

Fibrinogen levels were elevated significantly in patients with versus without complications, with versus without hypertension, with versus without obesity, and with type II versus type I diabetes. Furthermore, compared with control subjects, the mean fibrinogen levels in patients with type I diabetes and in those without complications were significantly higher ($P < 0.005$), whereas the age ranges were similar in these three groups.

Table 3 presents a comparison of various clinical characteristics between the diabetic patients without (group A) and those with (group B) vascular complications. The patients in group B were significantly older and had longer duration of diabetes. Their mean glucose levels were marginally higher and their HbA_1 levels significantly higher. The mean cholesterol levels, but neither the triglycerides nor HDL cholesterol levels, were elevated significantly in group B. No significant differences were observed in factor VII activity. However, CRP concentration, an acute-phase protein, was elevated marginally in this group.

Correlations between fibrinogen and continuous variables

Univariate regressions between fibrinogen and the variables described in Table 3 are shown in Table 4. Correlations between fibrinogen and age, cholesterol,

Table 3—*Comparisons of continuous variables between patients without (group A) and with (group B) vascular complications*

	Group A (N = 57)	Group B (N = 59)	P
Age (yr)	50.9 ± 1.9	62.0 ± 1.9	0.0001
Duration of diabetes (yr)	9.0 ± 1.1	15.2 ± 1.4	0.0004
Plasma glucose (mg/dl)	194 ± 12	226 ± 11	0.051
HbA_1 (%)	10.2 ± 0.28	11.10 ± 0.26	0.028
Cholesterol (mg/dl)	199.0 ± 5.9	226.0 ± 5.9	0.0015
Triglycerides (mg/dl)	210 ± 25	237 ± 27	0.47
HDL cholesterol (mg/dl)	53.0 ± 2.3	50.0 ± 2.8	0.36
Factor VII (%)*	115.0 ± 5.5	121.0 ± 7.3	0.47
CRP (mg/dl)*	1.84 ± 0.59	3.70 ± 0.76	0.06
Fibrinogen (mg/dl)†	307.0 ± 9.3	369.0 ± 9.8	<0.0001

Values are means ± SE.
*$n = 31$ (group A) and $n = 25$ (group B).
†$P < 0.0001$ vs. control subjects.

Table 4—*Univariate correlation coefficients between fibrinogen and continuous variables*

	N	MEAN ± SE	R	P
AGE (YR)	116	56.6 ± 1.44	0.41	<0.001
DURATION OF DIABETES (YR)	116	12.2 ± 0.9	0.13	0.18
PLASMA GLUCOSE (MG/DL)	116	210.00 ± 8.24	0.05	0.60
HbA_1 (%)	116	10.7 ± 0.2	0.18	0.049
CHOLESTEROL (MG/DL)	106	212.0 ± 4.4	0.29	0.002
TRIGLYCERIDES (MG/DL)	106	223.0 ± 18.2	0.14	0.16
HDL CHOLESTEROL (MG/DL)	88	51.4 ± 1.8	0.17	0.12
FACTOR VII (%)	56	118.0 ± 4.4	0.29	0.032
CRP (MG/DL)	56	2.68 ± 0.49	0.50	<0.001

and CRP were significant. A weak but significant correlation also was observed with factor VII activity and HbA_1.

Stepwise multiple regression analyses

In view of the potential interdependence of multiple variables such as age, duration and type of diabetes, glucose control, hypertension, and vascular complications, stepwise multiple regression analyses were performed to identify significant independent determinants for fibrinogen (Table 5) and vascular complications (Table 6) separately. Of the 14 variables examined, the presence of vascular complications and type II diabetes contributed almost equally as determinants of fibrinogen. Together, these two variables accounted for ~30% of the variability in fibrinogen ($r^2 = 0.2953$, $P < 0.0005$). Addition of all other variables including age, duration of diabetes, and diabetes control to the model did not change the power of predicting fibrinogen significantly. Regarding vascular complications (Table 6), fibrinogen and hypertension were individually significant determinants ($r^2 = 0.16$ and 0.15, respectively; $P < 0.002$). Duration, by itself, was a relatively minor determinant ($r^2 = 0.078$); however, addition of duration to fibrinogen or hypertension raised their predictive power to ~23% ($P = 0.001$). Together, these three variables could account for ~28% of the predictability for complications ($P <$ 0.01), which was not much improved by considering cholesterol, HbA_1, or any of the other variables in the model.

CONCLUSIONS— The search for the factor(s) underlying accelerated atherosclerosis in diabetes continues. It is clear that traditional risk factors, e.g., age, hyperlipidemia, smoking, hypertension, and obesity do not explain this accelerated risk (11,12). Other potential candidates include platelet hypersensitivity (24), coagulation factors (25), and perhaps endothelial cellular dysfunction (26). The incriminatory evidence for these additional mechanisms is, as yet, far from conclusive.

In this study, we attempted to explore further the prevalence and role of hyperfibrinogenemia in relation to diabetic vascular disease, in view of the existing epidemiological evidence in general populations (1–4). A role for fibrinogen in the pathophysiology of diabetes was suggested by the reports of *1*) hyperfibrinogenemia in cross-sectional studies, albeit in a small number of patients (14–18); 2) impaired fibrinolysis at rest and/or after physical training in several, but not all, studies (8,18,25,27); 3) enhanced generation of fibrin degradation products (28,29); 4) inhibition of antithrombin III activity by nonenzymatic glycosylation, although in the setting of unphysiological glucose concentrations (30); and 5) reduced fibrinogen survival (28,31).

The results presented in this report indicate that fibrinogen concentrations frequently are elevated in diabetes, regardless of diabetes duration, but particularly in those with type II diabetes and preexisting vascular complications. However, even patients with type I diabetes and no clinically evident vascular complications had significantly elevated mean fibrinogen levels. Evidence for elevated fibrinogen concentrations before the onset of vascular disease is controversial, primarily because of difficulties in clinically assessing onset. In a small number of patients with >15 yr duration of type I diabetes, Coller et al. (16) found no appreciable increase in fibrinogen levels in those without retinopathy ($n = 8$), whereas those with retinopathy ($n = 21$) had striking elevations. Similarly, Jensen

Table 5—*Stepwise correlations of fibrinogen with various determinants in multiple regression analyses*

PARAMETER	ADJUSTED R^2
VASCULAR COMPLICATIONS	0.1600
DIABETES (TYPE II VS. TYPE I)	0.1868
VASCULAR COMPLICATIONS AND TYPE OF DIABETES	0.2953
VASCULAR COMPLICATION AND TYPE OF DIABETES AND DURATION	0.2950
VASCULAR COMPLICATIONS AND TYPE OF DIABETES AND HbA_1	0.2960
VASCULAR COMPLICATIONS, TYPE OF DIABETES AND DURATION, HbA_1, AND OBESITY	0.3050
ALL	0.2710

Other parameters entered in analyses included cholesterol, triglycerides, HDL cholesterol, age, sex, glucose, type of treatment, smoking, and hypertension.

Table 6—*Stepwise correlations of presence of vascular complications with various determinants in multiple regression analyses*

Parameters	Adjusted r^2
Fibrinogen	0.1556
Hypertension	0.1540
Duration	0.0780
Fibrinogen and hypertension	0.2330
Fibrinogen and duration of diabetes	0.2301
Hypertension and duration of diabetes	0.1980
Fibrinogen, hypertension, and duration of diabetes	0.2750
Fibrinogen, hypertension, duration of diabetes, and HbA_1	0.2790
Fibrinogen, hypertension, duration of diabetes, HbA_1, and cholesterol	0.2970
All	0.2480

Other parameters entered in analyses included age, sex, triglycerides, HDL cholesterol, glucose, type of treatment, obesity, smoking, and type of diabetes.

et al. (32) reported a progressive increase in fibrinogen levels with increasing severity of proteinuria compared with those with no proteinuria. On the other hand, fibrin degradation products were elevated markedly in newly diagnosed type I patients in another report (29), and elevated fibrinogen levels were documented even in mildly glucose intolerant diabetic patients by McMillan et al. (17). Taken together, these observations and ours support the view that fibrinogen excess might contribute not only to the vessel wall pathology (5,6), but it may even exacerbate the diabetic vasculopathy, rather than simply being a marker for preexisting disease.

Another important issue is the relationship of fibrinogen levels with hyperglycemia. We found no significant correlations between fibrinogen and ambient plasma glucose levels or HbA_1 levels, and these two indexes of diabetes control did not have any discernible impact on the prediction of fibrinogen in multiple regression model (Table 5). However, note that Jones et al. (28,31) found that shortened fibrinogen survival was reversible by correction of hyperglycemia. Therefore, it is possible that acute fluctuations in glycemia play an important role in thrombin activation in the presence of elevated fibrinogen concentrations.

Of considerable interest are the findings in our study of the relationship of fibrinogen with vascular complications (Tables 3 and 6). Not surprisingly, the patients with complications (group B) were older, had longer duration of diabetes, poorer control, and higher cholesterol levels. The mean fibrinogen level in this group was 50% greater compared with control subjects, and 20% greater compared with the group without complications. Factor VII activity level, related to cardiovascular events in some studies (2,33) and found to be elevated in patients with diabetes in some but not all studies (25), was not elevated in our study. Factor VII activity seems to be influenced by numerous dietary, hormonal, and other factors (34), and our study was not designed to address this issue. On the other hand, CRP, also an acute-phase reactant, was elevated marginally in our patients with complications. In view of the interdependence of multiple predictors of vascular complications, the stepwise correlations in multiple regression analyses (Table 6) are of particular interest. As indicated by these analyses, vascular complications correlated best with only 3 of 14 factors entered in this model, i.e., fibrinogen, hypertension, and duration of diabetes. Individually, fibrinogen appears to be as important as hypertension, and, together, these three variables account for ~30% of the predictability of the presence of vascular complications. Interestingly, glucose control and none of the lipid parameters examined added significantly to the adjusted correlation coefficients, even though mean levels of glucose, HbA_1, and cholesterol were elevated significantly in patients with vascular complications. Whether fibrinogen is related deferentially to micro- or macrovascular complications cannot be determined from these data, because the number of patients with microvascular disease alone was relatively small. The prognostic significance of hyperfibrinogenemia in diabetes can be determined only by prospective studies. If fibrinogen proves to be a risk factor in diabetic vascular disease, then further efforts to investigate the possibilities of therapeutic interventions (27,35) will be warranted.

In summary, our studies suggest that hyperfibrinogenemia may be one of the important missing links in the pathogenesis of diabetic vascular disease. Hyperfibrinogenemia is particularly prevalent in type II diabetes, and along with hypertension and duration of diabetes, it may be a major independent predictor of vascular complications. Future studies of pathogenesis and prevention of diabetic vascular disease should be designed to evaluate the role of fibrinogen, among other known and potential risk factors.

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