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Plasma Factor XIII in Patients with Diabetic Angiopathy

TAYSSIR K. EYADA, M.D.; HODA A. SADEK, M.D.;
IBRAHIM K. EYADA, M.D.; GAMAL SAADY, M.D.
and SANEYA KAMEL, M.D.

The Departments of Clinical Pathology, Surgery and Medicine, Faculty of Medicine, Cairo University.

Abstract

Plasma factor XIII was estimated in 30 diabetic patients with angiopathy and in 10 healthy individuals with matched age and sex as a control group. There was a highly significant increase in factor XIII activity in plasma of diabetic patients which might promote intravascular and endoparietal fibrin deposition and may contribute to the development of atherosclerotic complications. Fasting blood sugar, age of the patient, duration of the disease had no influence on factor XII activity.

Introduction

SINCE persons with diabetes live longer, they are at increased risk for the development of chronic complications of diabetes including the vascular complication of micro-and macro-angiopathy. As haemostatic abnormalities are common in diabetic patients, it is thought that the impaired balance between coagulation and fibrinolysis encourage hypercoagulable tendency and lead to intravascular fibrin deposition which can contribute to the development of vascular complications[1].

Fibrin deposition and its organization markedly depend on Factor XIII action[2]. Since intravascular and endoparietal fibrin deposition is thought to be involved in the development of atherosclerosis, F XIII activity is measured in 30 diabetic patients with both micro-and macroangiopathy.

Material and Methods

A) Patients group :

This group included 30 non insulin dependent diabetic patients with both micro and macro-angiopathy. They were 20 males and 10 females.

Their ages ranged between 35-76 years with a mean of 58.8 ± 9.8 y. The diagnosis of micro-angiopathy was based on

the existence of diabetic retinopathy. The criterion for macroangiopathy was the presence of one or more out of the following conditions : Arterial hypertension, chronic coronary insufficiency, chronic peripheral arterial occlusive disease.

Patients with hepatic or renal disorders or taking any medications known to have an influence on coagulation and fibrinolytic system were excluded from the study.

B) Control group :

This group included 10 normal subjects with matched age and sex. Their ages ranged between 35-75 years (mean 51.1 ± 12.16). They were 5 males and 5 females.

All cases were subjected to full clinical history and examination and to the following investigations :

— Fasting blood sugar : by the enzymatic method.

– Factor XIII estimation by using coagulation factor XIII rapid reagent of Behringwerke[3].

Principle :

The plasma sample is serially diluted with factor XIII reagent solution. Portions of the dilutions are incubated with cothrombin kaolin at 37°C and coagulated. After 10 min the clots are mixed with 5% monochloracetic acid and tested for factor XIII activity : Stabilized clots remain solid, non-stabilized clots are dissolved. The greater the factor XIII concentration of the samples, the higher the dilution in which an insoluble clot is still formed. With this method it is possible to perform both screening tests and quantitative determinations.

Normal range :

Normal range from 70-130% of the normal.

Statistical analysis of comparisons between groups was done using Fischer's test and ANOVA analysis of results.

Results

Table (1) Demonstrates clinical and laboratory data of diabetic patients with angiopathy.

This group included 30 patients, 20 males and 10 females. Their ages ranged between 35-76 years with a mean of 58.8 ± 9.8 y.

Their fasting blood sugar ranged between 150-257 mg/dl with a mean value of 198.26 mg/dl ± 33.

Factor XIII activity ranged between 200%-400% with a mean value of 306.6% ± 101.5.

Table (2) Demonstrates statistical comparison of mean between control group and diabetic group as regard fasting blood sugar and factor XIII concentration.

The fasting blood sugar of the control group ranged between 65-90 mg/dl with a mean value of 79 ± 9.37.

Factor XIII activity ranged between 50% and 100% with a mean value of 85% ± 24.15.

No correlation was observed between factor XIII and age as well as between factor XIII and fasting blood sugar and duration of the disease.

Discussion

One of the major complications of diabetes is the development of diabetic angiopathy (micro and macro) associated with arteriosclerosis and thrombosis.

In the present study diabetic patients with angiopathy had a significantly higher factor XIII activity as compared to age matched controls ($P < 0.001$).

This higher activity may be related to the metabolic abnormalities associated with diabetes mellitus. An altered plasma lipid composition in the form of hypercholesterolemia and hypertriglyceridaemia markedly enhance plasma factor XIII activity.

This is in agreement with Cucucanu et al.[**4**]. Also it has been suggested that there is increased production of factor XIII or transglutaminase by the liver as several enzymes thought to be synthesised by the liver have been shown to be increased in diabetic hyperlipaemic states as lecithin cholesterol acyl transferase, gamma glutamyl transpeptidases as well as pseudocholinesterases[**5**].

Factor XIII is a fibrin stabilizing factor, it forms a covalent linkage between plasmin inhibitor and fibrin which contribute significantly to the stabilitty of fibrin clot and the development of atherosclerotic process.

Christe et al.[**6**] reported that in diabetic angiopathy enhancement of factor XIII activity and concentration concomitant with high fibrinogen level, increased serine protease inhibitor concentration together with impaired fibrinolysis found in diabetic patients all working together will promote intravascular and endoparietal fibrin deposition and thus contribute to the development of atherosclerotic process.

In previous works in order to explore the disturbances in the coagulation-fibrinolytic system in diabetics with micro and macro angiopathies we have measured factor VIII, vWF[**7**], FDPS, fibronectin[**8**], and antithrombin III[**9**]. The changes observed together with the increased factor XIII activity reflect a general alteration in haemostasis in diabetes mellitus. Atherosclerosis leads to thickening of capillary walls and even venular walls which will lead to development of signs and symptoms of vascular system affection according to the vessel affected.

If this microangiopathic lesion affect retinal precapillary arterioles this will lead to regional ischaemia which is compensated for by increased blood flow by autoregulatory mechanism. This will result in the formation of micro-aneurysms with progression of the disease, the retinal hypoxia increases and new vessels formation occurs[**10**].

Atherosclerosis of coronary arteries, cerebral arteries and arteries of lower limbs will lead to coronary heart diseases, myocardial infarction, cerebral haemorrhage and intermittent claudication respectively.

Table (1) : Clinical and Laboratory Data of Diabetic Patients with Angiopathy.

No.	Age	Sex	Duration of the disease	Diagnosis	F.B.S. m/dl	F. XIII Conc. %
1	56	Male	6 years	Coronary insufficiency	200	200%
2	60	Male	10 years	Retinopathy	160	400%
3	57	Male	8 years	Hypertension	180	440%
4	50	Male	5 years	Coronary. I	150	200%
5	69	Male	10 years	C.I + Retinopathy + Hypertension	240	400%
6	75	Male	15 years	C.I + Retinopathy + Hypertension + PAOD	210 257	400%
7	60	Male	8 years	C.I + PAOD C.I.	186 150	400%
8	55	Male	5 years	C.I.	180	200%
9	45	Male	5 years	Hypertension	190	200%
10	36	Male	4 years	C.I. + Retino.	180	200%
11	65	Male	9 years	C.I + PAOD	240	200%
12	70	Male	10 years	C.I. + POD + hypertension	270	200%
13	57	Male	7 years	Hypertension + Retinopathy	215	400%
14	62	Male	12 years	C.I. + PAOD arterial		400%
15	60	Male	10 years	Occlusive disease Hypertension + Retinopathy	180 150	400%

16	62	Male	6 years	C.I.	190	200%
17	55	Male	5 years	C.I. + Retinopathy + PAOD	170	200%
18	76	Male	10 years	C.I. + Retinopathy + PAOD	190	400%
19	65	Male	9 years	C.I.	190	400%
20	55	Male	5 years	Hypertension + Retinopathy	170	200%
21	60	Female	10 years	C.I. + PAOD	220	200%
22	58	Female	8 years	Hypertension	210	400%
23	35	Female	5 years	C.I.	200	400%
24	45	Female	6 years	C.I. and Retinopathy	230	200%
25	67	Female	8 years	C.I. and Hypertension	225	400%
26	65	Female	11 years	Retinopathy	150	200%
27	55	Female	5 years	C.I., Hypertension + PAOD	230	400%
28	72	Female	12 years	C.I. + PAOD	235	200%
29	57	Female	7 years	C.I., Hypertension		400%
30	60	Female	10 years			400%
Mean	58.8		8.03 ± 2.70		198.26	306.6 ±
S.D	± 9.8				± 33	101.5

CI : Coronary insufficiency.

PAOD : Peripheral arterial occlusive diseases.

Table (2) : Comparison between Control Group and Diabetic Group as Regard F.B.S. and F. XIII Concentration.

Group	No.		F.B.S.	F. XIII Conc.
Control	10	Mean	79	85
Diabetic		S.D	± 9.37	± 24.15
	30	Mean	198.26	306.6
ANOVA		S.D	± 33	101.5
results			12.4	17.66
P value			< 0.001	< 0.001

ANOVA : Analysis of variances.

No correlation was found between factor XIII and age as well as factor XIII with fasting blood sugar and duration of the disease indicating that these two parameters had no influence on factor XIII activity.

Therefore haemostatic abnormalities regarding F. XIII is present in diabetic patients with angiopathy and thus encourage tendency to hypercoagulability which contribute to the vascular complications found in diabetics.

Much work remains to be done in this field like estimation of subunit A and B of factor XIII. Estimation of subunit A may coincide with higher factor XIII concentration in diabetic patient with angiopathy as subunit A is responsible for the overall solubility of fibrin and its deposition which may contribute to hypercoagulability of the vascular complications present in diabetes.

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