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Fibronectin (FN) As an Important Parameter of Hypercoagulability in Patients on Regular Haemodialysis Treatment (RDT)

MOHAMED G. ELDIN SAADI, M.D.; TAYSSIR K. EYADA, M.D.; AMIN R. SOLIMAN, M.D.; USAMA A. SHARAF ELDIN, M.D. and MOHAMED H. HAFEZ, M.D.

The Departments of Internal Medicine & Nephrology and Clinical Pathology, Faculty of Medicine, Cairo University.

Abstract

FN is a glycoprotein present in body fluids and tissues and is known to have a binding property involved in the haemostatic mechanism among other functions. FN is known to be low in chronic renal failure (CAF) patients undergoing RDT. Whether it plays any role in the hyeprcoagulability of some such patients; particularly clotting in the hollow fibre is not known. FN was studied in 12 CRF patients on RDT having hypercoagulability and requiring higher heparin doses, also in 12 similar patients with no coagulation problems and receiving usual heparin doses and in 10 normal controls. In all the patients the examined coagulation tests were within the normal ranges and showed no significant differences among the patients groups. AT III was significantly higher in the hypercoagulability group than the healthy controls and insignificantly higher than normal RDT group. Plasma FN in the normal heparin group (240.8±89.5 mg/L) was significantly lower than in the control cases (365±39.4 mg/L) $p<0.001$. The level in the hypercoagulability group (555.8±202.14 mg/L) was significantly higher than the level in healthy controls $p<0.005$, and consequently more significantly higher than the normal heparin group $p< 0.001$. FN was above the normal range in 8/12 cases with hypercoaulability suggesting an important role in inducing coagualtion and/or antagonising the anti-coagulation.

Introduction

EXPOSURE of blood to a foreign surface induces protein adsorption, adhesion of the platelets, leukocytes, and red blood cells, with consequent activation of coagulation [1].

Prevention of extracorporeal thrombosis during haemodialysis is routinely achieved by heparinisation. The dose of heparin requried varies among patients; for reasons that are not completely understood; each requiring a different heparin profile. Occasional clotting of blood in the dialyser still remains to be a common complication [2].

Several factors may be involved in the failrue of heparin to achieve prevention of

extracorporeal thrombosis during haemodialysis.

The metabolic state of the patient may alter his heparin requirement as the heparinised blood would clot more readily in the presence of acidosis [3].

Heparin exerts its anti-coagulant effect by various actions including the enhancement of anti-thrombin III (AT III). Consequently the level of AT III may influence the efficiency of heparin [4].

Heparin is also known to reduce platelet aggregability and to induce thrombocytopenia. Yet several investigators demonstrated that heparin in concentrations used during haemodialysis might enhance platelet adherence to the dialyser membrane and potentiate platelet aggregability by ADP and adrenaline [5,6 & 8].

Platelet factor 4 (PF4) released from adherent platelets would neutralize the anti-coagulant effect of heparin, necessitating larger doses to maintain effective anticoagulation. PF4 being non-dialysable may achieve a higher level in RDT patients [8].

FN is one of the factors involved in the haemostatic mechanism [9 & 10]. Plasma FN concentration in CRF patients under conservative treatment or receiving RDT was reported to be significantly lower than in normal healthy controls [11,12 & 13]. It has not yet been studied as a factor which might have a role in this coagulation process induced by dialysis.

The aim of the work was to measure the predialysis coagualtin profile and plasma FN level in CRF patients under RDT and who have frequent hypercoagulation problems, mainly dialyser thrombosis and to compare these with a similar group of patients without such complications.

Material and Methods

The study included 3 groups. The first group included 12 CRF patients on RDT who underwent frequent extracorporeal thrombsois during dialysis and receive higher heparin doses on dialysis. The second group included 12 CRF patients on RDT who receive usual heparin doses on dialysis. The third group included 10 normal healthy controls.

The samples from the patients were taken before a dialysis sitting and were tested for:

- Coagulation profile comprising clotting time (CT) using the Lee and White method, activated partial thromboplastin time (APTT), bleeding time (BT) using Duke method and platelet count.
- Plasma firbonogen level.
- Plasma AT III was quantitatively measured by the single radial immunodiffusion technique using agarose norpartigen plates with monospccific antiserum supplied by Behring company [14].
- Plasma FN was quantitatively determined using the commercially prepared immunodiffusion plates provided by Behring company [15].
- Serum albumin and globulin levels.

The control samples were tested for AT III and FN

The results were analyzed for statistical comparison using the Student "*t*" test of significance [16].

Results

Results are shown in tables 1-4.

Table (1): Clinical and Laboratory Data of RDT Patients with Dialysis Hypercoagulability.

No.	Sex and Age (years)	Original disease	DRT Duration (months)	Serum Creatinine 53-106 μ/mol/L	Heparin Units/ Session	Platelet Countl 50-400,000/ c.mm.	B.T. (Duke) 4-7 min	C.T. (Lee & White) 5-10 min	A.P.T.T. 32-42 sec	Fibrinogen 2-4 g/L	Albumen 32-45 g/L	Globulin 23-35 g/L	AT III 210-310 mg/L	FN 200-400 mg/L
1	M42	C.G.N.	72	972.4	15000	200000	5	7	32	2.5	32	38	3.42	650
2	M38	C.P.N.	84	884	15000	190000	4	6	28	2.95	36	33	849.3	300
3	M55	C.G.N.	12	751.4	17500	230000	2.15"	6.15"	33	2.3	34	28	461.1	600
4	M58	E.S.R.D.	12	795.6	13750	250000	5	9	26	1.7	38	36.4	498	800
5	M56	E.S.R.D.	12	928.2	15000	190000	5.10"	7	29	1.05	27.5	58.5	456	600
6	M23	C.G.N.	24	1034.3	12500	220000	3.30"	7	49	2.55	48	35	375	870
7	M42	C.G.N.	60	1060.8	12500	210000	3	9	30	2.6	41	43	802.5	400
8	M38	C.G.N.	72	707.2	15000	220000	3	3	39	3	35	40	405.4	340
9	M29	C.P.N.	108	884	15000	170000	4	6	36	2.8	26.5	29.5	482	440
10	F28	C.P.N.	36	707.2	12500	186000	3.30"	10	40	4	35.5	35.5	230	370
11	M40	C.G.N.	24	839.8	12500	210000	1.30"	7.30"	31	2	34	36	550	850
12	F60	C.P.N.	18	795.6	12500	195000	2.50"	4	26	2.8	36	40	396	360
M	42.4±		44.5	863.4±	14062.5	205916.7	3.34"	6.49"	33.25	2.25±	35.3±	37.7±	487.28±	555.8±
S.D	12.45		±33.2	119.16	±1610.1	±21952.3	±1.8"	±2.1"	±6.76	0.73	5.68	7.81	178.66	202.14

Table (2): Clinical and Laboratory Data of RDT Patients with Normal Hypercoagulability.

No.	Sex and Age (years)	Original disease	DRT Duration (months)	Serum Creatinine 53-106 µ/mol/L	Heparin Units/ Session	Platelet Countl 50-400,000/ c.mm.	B.T. (Duke) 4-7 min	C.T. (Lee & White) 5-10 min	A.P.T.T. 32-42 sec	Fibrinogen 2-4 g/L	Albumen 32-45 g/L	Globulin 23-35 g/L	AT III 210-310 mg/L	FN 200-410 mg/L
1	M24	E.S.R.D.	24	795.6	10000	200000	3.30"	6	29	2.4	42.6	33	258	320
2	M53	P.C.K.	6	928.2	10000	332000	2.30"	4.30"	53	3.5	37	31.4	375	180
3	M35	C.P.N.	12	795.6	10000	190000	3.10"	2.50"	30	2.7	22	27.5	548.5	250
4	F46	C.P.N.	24	777.9	10000	253000	2	11.30"	40	3.3	38.5	38.5	300	40
5	M32	C.G.N.	9	848.6	10000	190000	3.40"	5.13"	35	3	28	54.5	286	275
6	F48	C.P.N.	108	990.1	10000	250000	4.15"	9	39	2.9	39.6	58.4	498	320
7	M56	E.S.R.D.	36	884	10000	190000	2	6	27	3.2	44	36	321	125
8	M22	C.G.N.	18	972.4	10000	166000	1.30"	8.30"	49	3	35	45	562.8	230
9	M29	C.G.N.	6	839.8	10000	200000	2.50"	7.15"	33	2.85	37	33	375	250
10	F22	C.G.N.	12	795.6	10000	180000	3	6	45	2.6	30	34	508	290
11	M43	C.G.N.	24	937	10000	120000	5	8	39	5.2	40	42	244	360
12	F38	C.P.N.	36	866.3	10000	210000	4	5	33	2.8	33	32	375	250
M	38.83		26.25	869.26	10000±	215916.7	3.27"	6.39"±	37.7±	3.12±	35.6±	38.8±	387.6±1	240.8±
S.D	±11.2			±73.5	0	±45275.8	±1.1"	2.20"	8.12	0.72	6.4	9.6	14.3	89.5

Table (3): Laboratory Data in Normal Controls.

No.	Sex.	Age (Years)	ATIII 210-310 mg/L	FN 200-400 mg/L
1	M	43	400	330
2	M	32	370	320
3	M	32	320	335
4	F	30	360	330
5	M	49	280	370
6	M	38	360	430
7	F	52	320	400
8	M	59	340	420
9	M	49	280	355
10	M	49	300	360
M		43.3	333	365±
S.D.		±9.9	±40	39.4

Table(4): Statistical Comparison of Studied Group.

	RDT Hyper-Coagual-bility n=12	RDT Normal Coag-ulability n=12	Healthy Controls n=10
Heparin M	14062.5	10000	
S.D.	±1610.1	+0	
t # normal RDT	8.7408		
P	<0.001		
ATIII M	487.28±	387.6	333
S.D.	178.66	±114.3	±40
t # control	2.9040	1.5450	
p	<0.01	N.S.	
t # RDT	1.6264		
p	N.S.		
FN M	555.8	240.8±	365
S.D.	±202.14	89.5	±39.4
t # t control	3.2013	4.3307	
p	<0.005	<0.001	
t # normal RDT	4.939		
P	<0.001		

Discussion

FN is a high molecualr weight glycoprotein existing in two major forms which are in dynamic equilibrium. The first is the soluble form present in body fiuids and the other is the insoluble form present in the tissues. It is synthesized by the hepatocytes, platelets, endothelial cells, firboblasts and different cells of the reticuloendothelial system [17].

FN being a binding molecule explains most of its functions including its role in haemostatsis [18].

Several factors may be involved in the thrombogenic activity of FN, including its known action of inducing platelet aggregability. It was also believed to enhance red cell adhesiveness [9].

It was also reported that FN interacts with some glycosaminoglycans including heparin [19,20] and would thus oppose its activity.

Our group of patients with renal failrue on RDT requiring higher heparin doses during the dialysis sessions had a higher plasma FN level (555.8±202.14 mg/l) significantly higher than the control value (365±39.4 mg/L, $p < 0.005$) and the usual heparin RDT group (240.8±89.5 mg/L, $p < 0.001$). FN was above the normal range in 8/12 of the hypercoagulability group suggesting a pathogenic role of FN.

The cause of this paradoxical elevation of FN in some of the renal failrue patients on RDT is not clear, It might indicate a continuation of the inflammatory process responsible for their renal failrue, as the FN level was noticed to be higher in patients with nephrotic syndrome in whom the renal functions were not yet impaired and it is believed to be related to the com-

pensatory increase in hepatic protein synthesis [21].

The blood pressures of our patients with hypercoagulability were under control comparable to the usual heparin group. Their plasma AT III values were significantly higher than the control values (487.28±178.66 mg/L, 333±40 mg/L, $p<0.01$) and insignificantly higher than the normal heparin group (387.6±114.3 mg/L).

This is in contrast to the low AT III predialysis levels detected by other investigators [22,23] and is in favour of the hypothesis of excess hepatic protein synthesis in some of the patients on RDT.

On the other hand the high FN level might reflect an ongoing hypercoagulable tendency as it is known to be released from stimulated platelets [10, 24].

In conclusion, the predialysis plasma FN levels were generally found to be lower than normal in chronic renal failure patients undergoing RDT. Yet it might be elevated in some of these patients having hypercoagulability problems particularly extracorporeal thrombosis. This elevated FN might have a pathogenic role or is a simple reflection of the hypercoagulability encountered. We recommend that the coagualtion profile study for RDT patients should include plasma FN as one of its parameters.

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