Hemostatic changes in patients with chronic renal failure

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Abstract:

Background: Renal disease results in significant disorder of hemostasis (bleeding diathesis or hypercoagulable state).
Objectives: This study is to determine the changes in some hemostasis parameters in patients with chronic renal failure and identify the effect of dialysis on these changes.
Patients and Methods: seventy five patients with end stage chronic renal failure were collected from Baghdad hospital, a full detailed history and clinical examination were performed, 50 patients were on maintenance weekly hemodialysis, and 25 patients were without dialysis.
Result: Bleeding time was significantly higher in patients with chronic renal failure who didn't need any type of dialysis, positive D-Dimer test. In some patients, Platelet count, prothrombin time, thrombin time, fibrinogene level, activated partial thromboplastin time; all did not reach significant level between both groups of patients.
Conclusion: hemostatic changes are not uncommon in patients with chronic renal failure, affecting the different parameter hemostasis so it should be consider in the management of these patients.
Keywords: chronic renal failure, prothrombin time, Thrombin time, bleeding time, activated partial thromboplastin time.

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Introduction:

In chronic renal failure (CRF), in addition to the fluid, acid-base, and electrolytes imbalance due to the deprived renal function, lead to accumulation of circulating toxins and waste products, in particular the nitrogenous waste products that are normally excreted in to urine. The relationship between CRF and abnormal hemostasis has long been recognized with quite high morbidity rate, Bleeding is one of the main manifestations of the altered hemostasis system in CRF, it is usually presented as cutaneous type of bleeding, including easy bruising, ecchymosis, mucosal bleeding and less commonly, epistaxis and hematuria. Other serious bleeding such as gastrointestinal and genitourinary bleeding or subdural hematomas can also occur but less frequently.(1, 2, 3, 4) Thrombotic complications may also develop in CRF patients but with higher frequency in patients undergoing hemodialysis in which thrombosis of the arteriovenous fistula is the most common presentation. (5,6) Although the underlying pathophysiology of bleeding tendency in CRF is still not fully understood, impaired platelet function is thought to be one of the main causes. This acquired platelet dysfunction is due to both decreased platelet activation and impaired adhesion to vascular subendothelial cells. (7, 8, 9, 10, 11, 12) In addition, some coexisting factors may intensify bleeding complications in CRF patients, such as coagulopathies, the use of heparin with dialysis, and anatomical abnormality. (11)

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Patients, Materials and Methods:

A total of 75 patients with end stage CRF collected from the surgical Specialty Hospital, Al-Yarmouk Teaching Hospital, Al-Kadhimiya hospital and Baghdad Teaching Hospital enrolled in this study. A fully detailed history and clinical examination were performed, 50 of the patients were on maintenance weekly hemodialysis and 25 of the patients were without dialysis. Controls: A total of 25 age and sex matched healthy individuals with normal blood urea and serum creatinine was taken as control group. Sampling: The following tests were done for all patients: Automated measurement of platelet count, blood urea and creatinine level. Measurement (classical method) of the following test: Prothrombine time (PT), activated partial thromboplastine time (APTT), Thrombine time (TT), fibrinogen concentration level.Latex agglutination of D-Dimer. Bleeding time (BT) done by IVY's method.

Statistical Analyses:

Statistical analysis was performed using SPSS version 7.5 computer software (statistical package, for social science.) t-test and ANOVA test were used for the difference between two groups, and when ANOVA show significant difference. Further assessed by use of Bonferonni t- test, statistical significant between three groups P(Mann-Whitney).

Results:

The results presented in this study were based on the analysis of 25 healthy control subjects and 75 patients with an established renal failure, 50 of these patients were on regular haemodialysis and the remaining 25 were not in need of any form of dialysis. As shown in table 1, the age of patients with renal failure ranged between 17-73 years with a

mean of 35.3 (± 15) years for those not on dialysis and (17-68) years with mean 39.7 (± 12.2) years for those on dialysis. Male gender constitutes 36% and 60% of renal failure patients not on dialysis and those on dialysis respectively, table1.

Table 1: The age and gender of patients groups

	Patients on dialysis		Patients not on dialysis	
Age in years				
Range	17-73		17-68	
Mean	35.3		39.7	
Gender	No.	%	No.	%
Female	20	40	16	64
Male	30	60	9	36
Total	50	100	25	100

Table2: The comparison table of three study groups of patients.

	Patients on dialysis	Patients not on dialysis	Healthy controls (n=25)	P=0.001 (ANOVA)
Bleeding time(min)				
Range	2-12	2-14	2.3-4	
Mean	5.1	7.1	3.3	
SD	2.7	3.5	0.6	
Platelets count (X109/L)				P=0.001 (ANOVA)
Range	100-700	85-600	200-300	
Mean	247.9	160.1	270	
SD	111.1	102.1	50.3	
Prothrombin time (PT) in sec				P = 0.17 [NS] (ANOVA)
Range	101-20	11-19	12-14	
Mean	14.7	14.6	13.1	
SD	2.4	2.8	0.7	
Partial thromboplastin time (APTT) in sec				P = 0.55[NS] (ANOVA)
Range	25-55	30-44	32-38	
Mean	36.1	34.7	35.3	
SD	6.4	4.3	1.9	
Thrombin time (TT) in sec				P = 0.003 (ANOVA)
Range	7-26	13-24	13-18	
Mean	16.5	18.8	15.6	
SD	3.2	2.7	1.77	
Fibrinogen conc,				P = 0.5[NS] (ANOVA)
Range	1-9.5	1.16-9.5	2.48-3.49	
Mean	3.7	3.7	3	
SD	1.8	2.0	0.3	
Total	50	25	25	

Bleeding time (BT) was prolonged (prolonged BT was consider if test time of measuring more than 4 min. of control group) in (28) patients, 14 of patients on regular dialysis and the other 14 patients without any dialysis, the mean level of BT was significantly higher in patients not on dialysis compared with both patients on dialysis and healthy control groups (P = 0.001) as shown in table 2. Regarding the mean of platelets count for patients on dialysis was (247.9 × 10^9/L), and (SD 111.1), while the mean of platelet count of patients not on dialysis (160.1 × 10^9/L) with (SD 102.1). The platelet count in patients not on dialysis is significantly lower than that mean of patients on regular dialysis at P value = 0.001 as shown in table 2. The total number of prolonged PT (Prolonged PT was consider if more than 5 sec. than control groups) was (8 from those not on dialysis and 13 on regular dialysis, this showed no significant statistical difference from control group. (p=0.17). As shown in table 2. Total number of prolonged APTT (Prolonged APTT was consider if more than 6 sec. than control groups) was 8 (one in those patients not on dialysis) with no significant difference from the control (p= 0.55). Total number of prolonged TT (Prolonged TT was considered if more than 6 sec. than control groups)was 16 patients (10 in those without dialysis, and 6 patients on regular dialysis) the mean TT was significantly higher in patients not on dialysis compared to those on dialysis and control group. (p= 0.003). The fibrinogen level was prolonged (Prolonged fibrinogen was consider if more than 4 g/L)in patients on dialysis (17 from 50 patients) and patients without dialysis (9 from 25 patients), the mean level was slightly higher in patients than control group (3.7 g/L , 3 g/L) respectively, however, the difference did not reach significant level (P = 0.5), as shown in table 2. The D-Dimer test was positive in two patients (8%) not on dialysis, and (6) patients (12%) on dialysis as shown in table 3 and 4.

Table 3: The deference in median D-Dimer concentration between three study groups.

	Patients on dialysis		Patients not on dialysis		Healthy control	
D-Dimer test	N	%	N	%	N	%
Negative (<0.5)	37	74	19	76	25	100
Equivocal (0.5-1)	7	14	4	16	0	0
Positive (>1)	6	12	2	8	0	0
Total	50	100	25	100	25	100

Table 4: The Positivity of D-Dimer test in patients groups.

	Patients on dialysis No. (%)	Patients not on dialysis No. (%)	Total No. No. (%)
Positive D-Dimer	6 (12%)	2 (8%)	8 (10.7)
Negative D-Dimer)	44 (88%)	23 (92%)	67 (89.3)
Total No. of patients	50 (100%)	25 (100%)	75 (100)

Discussion:

Patients with CRF have an increased incidence of bleeding tendency, that is recognized clinically as purpura, epistaxis, gingival bleeding and GIT bleeding. In general, the severity of bleeding diathesis parallels the degree of azotemia. The pathophysiology of bleeding diathesis is complex and appears to involve abnormalities in both platelet function and coagulation as well as thrombocytopenia in some patients (9). In impaired

platelet function, the mechanism is multifactorial. Anemia that accompany renal insufficiency, the presence of an unidentified inhibitor, and presumably circulating toxin that are usually excreted by the kidney all lead to impairment of platelet function.This study shows that BT in patients not on dialysis was significantly higher than those on dialysis and this result agrees with that of Eberst & Brokowitz, this can be explained by dialysis improve platelet function if thrombocytopenia is excluded(12).Although it has been reported that hemodialysis (HD) and peritoneal dialysis (PD) were equally effective in improving the bleeding diathesis associated with uremia, however some studies reported that PD is superior to HD due to more effective removal of uremic toxins, because of fewer abnormalities in arachidonic acid metabolism, fewer adverse effect on platelet aggregation (because there is no contact with the dialysis membrane)(12).Moreover, some authors reported that HD itself disturb normal hemostatic function i.e. either depress or enhance platelet function in uremic patients(13). The hemostatic disadvantages associated with HD include activation of coagulation cascade, repeated exposure to heparin, increased incidence of acquired platelet storage pool defect, and modification of fibrinolytic system and the natural inhibitors of coagulation (12). It is well recognized that uremia may be associated with a bleeding tendency, prolongation of the skin capillary bleeding time is the best indicator of bleeding tendency. The role of dialysis in shortening bleeding time is attributed mostly to the elimination of uremic toxin which play an important role in platelets and endothelial dysfunction, an important one to be considered is the effect of nitric oxide (NO) which has the ability to impair interaction between platelet and vascular wall (12,14). In patients with renal failure, acquired deficiencies of coagulation factors can be present. The decrease in factors levels result from loss in the urine, sequestration in the kidney, and abnormal distribution due to change in intravascular volume, in addition to the uremic toxin inhibition of clotting factors and the use of low dose heparin during each session of HD. This explains the prolongation of PT, APTT and TT. (8,12,16,17) Patients with CRF show features compatible with chronic, and systemic inflammatory response. The increased plasma levels of inflammatory cytokines and acute phase reactant protein observed confirms this observation. Hyperfibrinogenemia is probably due to of non – specific inflammatory response to the disease (18,19), while hyperfibrinogenemia was less commonly encountered (8 patients), five of them were on dialysis, perhaps, resulting from repeated deposition of fibrin within dialyzer (20). Positive D-Dimer test was noticed in two patients not on dialysis and in six patients on regular dialysis. (all patients were free from any sort of thrombosis). Geodge et al. 1989 reported increased plasma concentration of D-Dimer in patients with CRF when compared with healthy control and suggested that D-Dimer is a useful marker of fibrin breakdown in renal failure (21). Experimental work has shown that vascular injury and thrombosis occurs within the glomerulus leading to FGS, and in patients with CRF a raised plasma PF4 was demonstrated in addition to a raised level of D-Dimer, which indicate intravascular platelet activation suggesting activation of hemostasis in these patients (21). In the current study appositive D-Dimer test was documented in (8) patients (10.6%) of the total & it was more commonly encountered in those on dialysis, due to increased release of t-PA induced by hemodialysis and consequent consumption of inhibitor which enhance the fibrinolysis activity during a hemodialysis , in addition to the effect of heparin used during the process(13,22,23,24).

Conclusion:

Bleeding time was significantly higher in patients of CRF who did not perform any type of dialysis, and also significantly higher in patients on regular dialysis compared with patients not on dialysis.

The frequency of positive D-Dimer test was higher in patients on dialysis compared to those without dialysis.

Authors' Contributions:

Harith Younis Serrheed: collected sample, and measuring the data with discussion.

Eman Jassim Mohammed AL-AKAM: statistical analysis of data and result, participated with discussion and conclusion.

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