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EVALUATION OF SOME HEMOSTATIC ABNORMALITIES IN CHRONIC KIDNEY DISEASE PATIENTS PRE AND POST HEMODIALYSIS

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ABSTRACT

Background: Chronic kidney disease and hemodialysis associated with disturbance in hemostasis. Uremic toxins induced platelet dysfunction, coagulopathy, endothelial dysfunction and impaired fibrinolysis. **Aim:** To evaluate some hemostatic abnormalities in patients with chronic kidney disease before and after hemodialysis. **Patients and methods:** A case-control study, involving (50) patients with chronic kidney disease on regular hemodialysis admitted to Ibn-Sina Teaching Hospital in Mosul city between April to September 2025, and (30) healthy controls. The sample underwent hemostatic investigations (pre and post hemodialysis) including: prothrombin time, activated partial thromboplastin time, fibrinogen, D-dimer, factor VIII, and Von Willebrand factor. **Results:** The mean age was 50.96 years, including 66% male and 34% female, the M: F ratio is 1.9: 1. The mean of prothrombin time (after hemodialysis), activated partial thromboplastin time, fibrinogen, D-dimer, factor VIII and von Willebrand factor were significantly higher in patients with chronic kidney disease in comparison to control. The mean of prothrombin time, activated partial thromboplastin time, D-dimer, and factor VIII after hemodialysis were significantly higher than before hemodialysis with P-value of (0.000), (0.032), (0.040) and (0.002) respectively. There was statistically significant direct correlation between prothrombin time and glomerular filteration rate before dialysis (r= -283, p=0.046). There was negative statically significant correlation between activated partial thromboplastin time before dialysis with factor VIII (r=-0.502, p=0.000). **Conclusions:** the current study concluded that the hemostatic markers were further increased after hemodialysis, which increased risk of bleeding and thromboembolic events.

KEYWORDS: Chronic kidney disease, Hemodialysis, Factor VIII activity, Von Willebrand antigen.

INTRODUCTION

Chronic Kidney Disease (CKD) has emerged as a significant global health challenge, projected by the World Health Organization to become the fifth most common chronic disease by 2040.[1] Defined by a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m² or markers of kidney damage persisting for at least three months, CKD affects approximately 10-13.4% of the global population.[2,3] As the disease progresses toward end-stage kidney disease (ESKD), patients face a myriad of complications, among which hemostatic disturbances are particularly complex and life-threatening. These disturbances create a paradoxical environment where patients are simultaneously at high risk for both severe bleeding tendencies and thromboembolic events.[4,5]

The pathophysiology of hemostatic dysfunction in CKD is multifactorial. One of the primary drivers is the accumulation of uremic toxins, such as urea and guanidinosuccinic acid, which disrupt normal platelet function.[6] These toxins interfere with platelet adhesion and aggregation by stimulating endothelial nitric oxide and prostaglandin production, while also impairing calcium mobilization and reducing the release of essential aggregation factors like ADP and serotonin.[7]

Furthermore, the chronic anemia associated with CKD exacerbates bleeding risks; low hematocrit levels reduce the physical contact between platelets and the vessel wall, as platelets remain sequestered in the central blood flow rather than migrating to the periphery where they can initiate clotting.[8,9]

Conversely, CKD is also characterized by a hypercoagulable state. Chronic inflammation drives the liver to increase the production of acute-phase reactants, most notably fibrinogen.[10] While certain coagulation factors like IX and XI may be reduced, others—including factor VIII and von Willebrand factor (vWF)—are frequently elevated, promoting thrombosis.[11] This imbalance is further complicated by impaired fibrinolysis, often due to increased activity of plasminogen activator inhibitor-1 (PAI-1).[4]

Hemodialysis (HD), the primary treatment for ESKD, introduces additional hemostatic challenges. The procedure involves the interaction of blood with artificial dialysis membranes, which can trigger inflammatory responses and activate the complement system and leukocytes.[12] To prevent clotting within the extracorporeal circuit, anticoagulants like heparin are routinely administered. However, in the uremic environment, the use of heparin significantly amplifies the risk of hemorrhage.[11] Moreover, the physical process of dialysis causes fluid shifts and hemoconcentration, which can acutely alter the levels of coagulation markers.[10]

Recent researches[13-16], highlight the acute impact of the dialysis procedure itself. By evaluating hemostatic markers before and after HD, it was observed that markers such as prothrombin time (PT), activated partial thromboplastin time (aPTT), D-dimer, and factor VIII increase significantly following a dialysis session. These findings suggest that the hemodialysis process further activates the coagulation cascade and endothelial dysfunction, heightening the risk of thromboembolic complications immediately post-procedure.

Understanding these abnormalities is critical for clinical management. The direct correlation between GFR and hemostatic markers emphasizes that as kidney function declines, the hemostatic balance becomes increasingly fragile. Early intervention and careful monitoring of markers like Factor VIII and vWF are essential to mitigate the risks of both bleeding and thrombosis in this vulnerable population. By synthesizing hematological and biochemical data, clinicians can better tailor anticoagulation strategies and improve the overall prognosis for patients undergoing regular hemodialysis.[15,16] The study aimed to evaluate some hemostasis abnormalities in patients in maintains hemodialysis pre &post dialysis and to evaluate the effect of hemodialysis on these hemostatic abnormalities.

PATIENTS AND METHODS

Study design and Setting: This is a prospective case control study involving 50 patients with CKD pre and post hemodialysis admitted to Ibn Sina Teaching Hospital in Mosul city during the period between April 2025 and September 2025, involved collection of data, blood samples and laboratory investigations.

Sample selection: All patients in this study (fifty patients) were on, folic acid and vitamin D when indicated and on regular hemodialysis twice a week, with intravenous unfractionated heparin dose (5000 units) before start of hemodialysis, and they are diagnosed as chronic kidney disease (stage five) on hemodialysis (clinically and according to creatinine result and GFR). Thirty healthy individuals (matched sex and age), were included as control.

Ethical Consideration: The approval was obtained from Ministry of Health / Nineveh Health Department, Ibn-Sina Teaching Hospital, and the agreement was obtained from all patients before the interview.

METHODS

Inclusion criteria included Adult patients above 18 years. Patients with chronic kidney disease on regular hemodialysis. Those who aged below 18 years, patients with history of bleeding episodes, patients who are receiving anticoagulant for other disease, or antibiotics, patients with liver diseases, patient with active infection, patients with malignancy, patients who needed to get blood transfusion in the last 3 month were excluded from the study.

Clinical Assessment: A questionnaire was used for each individual include: person's name, age, sex, symptoms, time of diagnosis of CKD, time of starting dialysis and cause of renal failure, medical history, history of bleeding and duration, history of thromboembolic events, regime of treatment and history of use of anticoagulant drugs, we ask about past medical history, past drug history and family history of hemostatic disorder.

General and systemic examination were done to all cases. The patients underwent prothrombin time and international normalized ratio (INR), activated partial thromboplastin time, fibrinogen level, factor VIII measurement, von Willebrand factor assay, D-Dimer level, blood urea, serum creatnine and estimated of glomerular filtration rate (GFR) by 2021 CKD-EPI Creatinine equation.

Blood sampling and sample handling

Seven milliliters of peripheral venous blood were obtained from each patient before dialysis and two milliliters after dialysis by suitable venipuncture technique. The venous blood samples were collected using disposable syringe and was processed as follows.

The EDTA anticoagulated sample (3 milliliters), immediately inverted manually several times to ensure good mixing with anticoagulant. Blood sample are kept at room temperature to be used within less than one hour to perform blood count.

Two and half milliliters of drawn blood placed in trisodium citrate tube, and centrifuged at 2000 gm for 15 min. to obtain platelet – poor plasma (PPP) for coagulation tests. The rest of drawn blood were put in serum separating tubes allowed to clot at room temperature for 30 minutes then centrifuged at 2000 rpm for 20 minutes to obtain serum for biochemical investigations. Blood samples from healthy volunteers used as a control for.

Statistical analysis: Data collected during the study were summarized in a Microsoft Excel 2010 spread sheet. Statistical analysis was performed using the Statistical Package for the Social Sciences (IBM-SPSS 26). Categorical data were presented as frequencies and proportions while the numerical data expressed in means and standard deviations. The assessment of the association between the numerical data was done by using independent t test for the independent variables and the paired t –test for the dependent variables. The Pearson correlation coefficients were calculated to find the relation between the studied parameters. A p-value ≤ 0.05 was considered significant.

RESULTS

The current studied sample included 50 patients with chronic kidney disease and 30 healthy controls. Figure (1) show the age distribution of patients with chronic kidney disease. The mean age was (50.96±16.983) with a range of (18_ 75) years.

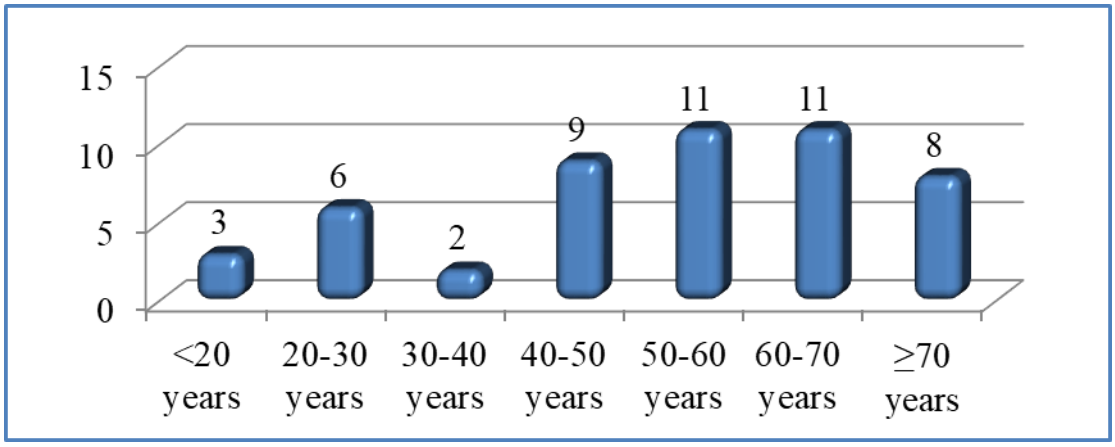

Figure (1): Distribution of the patients according to age.

Figure (2) show sex distribution of patients with chronic kidney disease in this study, out of 50 patients, 33 (66.0%) were males and 17 (34.0%) were females, M: F ratio is 1.9: 1.

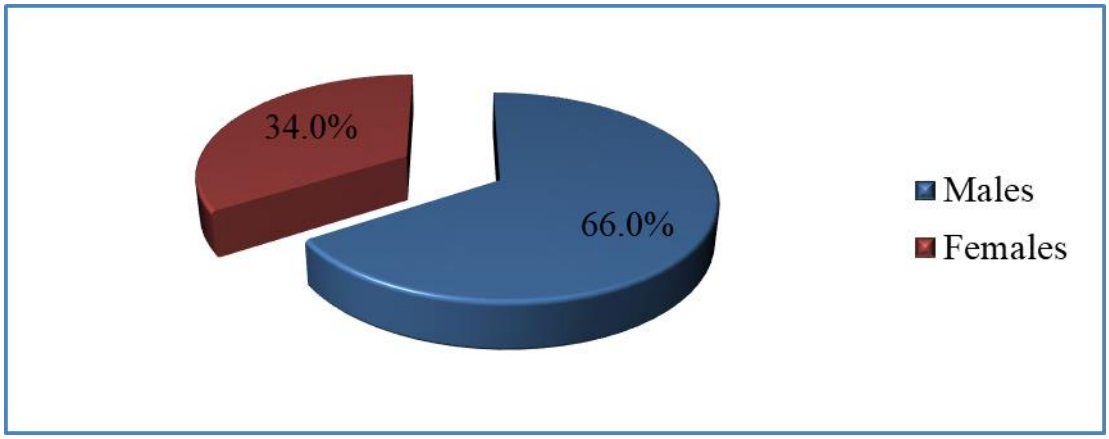

Figure (2): Distribution of the patients according to sex.

There were significant statistical differences between the mean APTT (35.08±5.465), Fibrinogen (3.39±0.502), D-dimer (1909.71±1982.776), FVIII (128.07±49.948) and VWF (352.69±379.224) among the cases before the dialysis in comparison to the controls with P value (0.000), (0.025), (0.007), (0.017), (0.002) respectively. After dialysis, all the hemostatic parameter had higher significant mean levels among the cases group in comparison to the control group, while PT before dialysis showed statically non-significant difference as shown in table (1).

Table (1): The effect of hemodialysis on hemostatic parameters before and after hemodialysis as compared to controls.

Hemostatic parameters		Studied groups		p-value
		Cases group	Control group	
		Mean±SD	Mean±SD	
Before dialysis	PT (S)	12.70±1.388	12.86±1.195	0.586
	APTT (S)	35.08±5.465	30.63±2.658	0.000
	Fibrinogen (g/l)	3.39±0.502	3.15±0.373	0.025
	D-dimer (ng/ml)	1909.71±1982.776	373.73±123.029	0.007
	FVIII (%)	128.07±49.948	103.23±31.754	0.017
	VWF (ng/ml)	352.69±379.224	116.81±28.073	0.002
After dialysis	PT (S)	13.48±1.343	12.86±1.195	0.043
	APTT (S)	36.50±4.621	30.63±2.658	0.000
	Fibrinogen (g/l)	3.44±0.479	3.15±0.373	0.000
	D-dimer (ng/ml)	5942.59±25700.212	373.73±123.029	0.000
	FVIII (%)	145.34±63.481	103.23±31.754	0.001
	VWF (ng/ml)	375.14±371.484	116.81±28.073	0.000
*Independent t-test for two means				

The mean level of PT, INR, APTT, D-dimer and FVIII among the patients before dialysis were significantly lower than after dialysis with P value (0.000), (0.000), (0.032), (0.040), (0.002) respectively. While the means of fibrinogen, and VWF showed no statistically significant differences between before and after dialysis, as shown in table (2).

Table 2: Comparison of hemostatic parameters among patients before and after dialysis.

Hemostatic parameters	Cases group		p-value
	Before dialysis	After dialysis	
	Mean±SD	Mean±SD	
PT (S)	12.70±1.388	13.48±1.343	0.000
INR	1.15±0.190	1.26±0.187	0.000
APTT (S)	35.08±5.465	36.50±4.621	0.032
Fibrinogen (g/l)	3.39±0.502	3.44±0.479	0.454
D-dimer (ng/ml)	1909.71±1982.776	5942.59±25700.212	0.040
FVIII (%)	128.07±49.948	145.34±63.481	0.002
VWF (ng/ml)	352.69±379.224	375.14±371.484	0.408
			***Paired t-test**

Before dialysis, there was no significant statistical correlations between the hemostatic parameters with blood urea and serum creatinine among patients. Fibrinogen demonstrated a positive trend toward correlation with S creatinine, however didn't reach statically significant P value, as shown in table (3).

Table (3): Correlations of hemostatic parameters with urea and serum creatinine among patients before dialysis.

Pearson correlation of Hemostatic parameters with urea and creatinine		r- value	Asymp. Std. Error	Approx. T	p-value
PT (S)	Blood urea (mg/dl)	0.089	0.147	0.620	0.538
	S. Creatinine (mg/l)	0.008	0.157	0.056	0.956
INR	Blood urea (mg/dl)	0.056	0.146	0.389	0.699
	S. Creatinine (mg/dl)	-0.063	0.174	-0.436	0.665
APTT (S)	Blood urea (mg/dl)	0.037	0.128	0.253	0.801
	S. Creatinine (mg/dl)	0.083	0.126	0.577	0.567
Fibrinogen (g/L)	Blood urea (mg/dl)	0.216	0.124	1.535	0.131
	S. Creatinine (mg/dl)	0.273	0.120	1.964	0.055
D-dimer (ng/ml)	Blood urea (mg/dl)	0.175	0.175	1.230	0.225
	S. Creatinine (mg/dl)	0.058	0.193	0.406	0.687
FVIII (%)	Blood urea (mg/dl)	0.126	0.129	0.877	0.385
	S. Creatinine (mg/dl)	0.063	0.111	0.440	0.662
VWF (ng/ml)	Blood urea (mg/dl)	-0.042	0.125	-0.294	0.770
	S. Creatinine (mg/dl)	0.084	0.134	0.586	0.560

Before dialysis the GFR was directly significantly correlated with PT and INR with P value (0.046) and (0.027) respectively, and the fibrinogen demonstrated a negative trend toward correlation with GFR, however didn't reach statically significant P value, as shown in table (4).

Table (4): Correlations of hemostatic parameters with GFR among patients before dialysis.

Pearson correlation of Hemostatic parameters with GFR	r- value	Asymp. Std. Error	Approx. T	p-value
PT (S)	0.283	0.114	2.046	0.046
INR	0.313	0.132	2.285	0.027
APTT (S)	0.070	0.097	0.483	0.631
Fibrinogen (g/l)	-0.264	0.114	-1.897	0.064
D-dimer (ng/ml)	0.110	0.172	0.765	0.448
FVIII (%)	-0.219	0.104	-1.552	0.127
VWF (ng/ml)	-0.022	0.148	-0.156	0.877

No statistically significant correlations were found between the urea and creatinine among patients after dialysis with the hemostatic parameters, as shown in table (5).

Table (5): Correlations of hemostatic parameters with urea and creatinine among patients after dialysis.

Pearson correlation of Hemostatic parameters with urea and creatinine		r- value	Asymp. Std. Error	Approx. T	p-value
PT (S)	Blood urea (mg/dl)	0.086	0.136	0.601	0.551
	S. Creatinine (mg/dl)	-0.103	0.135	-0.720	0.475
INR	Blood urea (mg/dl)	0.141	0.118	0.988	0.328
	S. Creatinine (mg/dl)	-0.059	0.122	-0.408	0.685
APTT (S)	Blood urea (mg/dl)	0.090	0.165	0.623	0.536
	S. Creatinine (mg/dl)	-0.002	0.156	-0.015	0.988
Fibrinogen (g/L)	Blood urea (mg/dl)	0.249	0.116	1.782	0.081
	S. Creatinine (mg/dl)	0.234	0.100	1.670	0.101
D-dimer (ng/ml)	Blood urea (mg/dl)	-0.011	0.029	-0.080	0.937
	S. Creatinine (mg/dl)	-0.206	0.096	-1.461	0.151
FVIII (%)	Blood urea (mg/dl)	0.101	0.117	0.705	0.484
	S. Creatinine (mg/dl)	0.101	0.104	0.702	0.486
VWF (ng/ml)	Blood urea (mg/dl)	-0.092	0.127	-0.640	0.525
	S. Creatinine (mg/dl)	0.179	0.133	1.260	0.214

After dialysis, there was no significant statistical correlations between hemostatic parameters with GFR, as shown in table (6).

Table (6): Correlations of hemostatic parameters with GFR among patients after dialysis.

Pearson correlation of Hemostatic parameters with GFR	r- value	Asymp. Std. Error	Approx. T	p-value
PT (S)	0.253	0.144	1.811	0.076
INR	0.196	0.137	1.386	0.172
APTT (S)	0.096	0.137	0.666	0.509
Fibrinogen (g/l)	-0.247	0.100	-1.764	0.084
D-dimer (ng/ml)	0.053	0.024	0.371	0.712
FVIII (%)	-0.142	0.123	-0.993	0.326
VWF (ng/ml)	-0.092	0.140	-0.637	0.527

DISCUSSION

Chronic kidney disease, particularly end-stage renal disease, involves irreversible renal function loss, leading to reduced glomerular filtration rate and uremic toxin accumulation. This condition necessitates renal replacement therapies like hemodialysis (HD), which, while prolonging patient survival, increases the risk of bleeding and thrombosis due to factors such as platelet dysfunction and the use of anticoagulants like heparin. Only a kidney transplant can effectively improve survival and correct endocrine dysfunction.[17]

In the current study, 50 adult patients with ESRD on regular hemodialysis (twice /week) were included before and after HD, the mean age is 50.96 years, including 66% male and 34% female, these finding consistent with Hernaningshi et al. study in Indonesia[18], that also included 50 patients with ESRD on hemodialysis, the

mean age was 51, with 56% males and 44% female. Other studies by Abo-Ghaneim et al. in Najaf the mean age was 46.7 years[19], by Abdelrahman et al. study in Eygpt the mean age was 55.2 years[20], by Alghythan et al. in Saudi Arabia the mean age was 50 years.[21] in all these studies male was predominance. While Kartikasari et al. study in Indonsia[22] was disagree with our result, which included 51 patient with CKD on hemodialysis the mean age was 49.71 years, but different in sex distribution, 49% males and 51% female.

In the current study, the APTT, fibrinogen, D-dimer, FVIII, and VWF before and after hemodialysis were significantly higher in patients in comparison to control with p value < 0.05 for all parameters. These findings are in agreement with those obtained by Palvo et al.[23], Jessica et al.[24] and Abdelrahman et al.[20] There are several possible explanations for these results, the prolongation of PT after HD develop due to uremic related coagulopathy (dysfunction or deficiency like factor II), hemodilution effect after HD.[23,25] The prolongation of APTT before HD due to the uremic coagulopathy. Whereas the prolongation of APTT after HD, in addition to previous cause is using heparin as the anticoagulant in HD procedure. Heparin binds to the enzyme inhibitor antithrombin III, which results in the inactivation of thrombin and other proteases involved in clotting of blood especially factor Xa and reduced activities of coagulation factors (factor II, IX, X, XII), these findings clear the effect of HD.[23,24,26] Fibrinogen level is elevated before HD due to chronic inflammation induced secretion of pro-inflammatory cytokines like interleukin 6 that increase production of fibrinogen from the liver, reduced its clearance via kidney, endothelial dysfunction, and elevated after HD, which has addition effect perse on these parameters due to fluid shift, hemoconcentration and inflammatory activation.[23,24,27] The level of D-dimer is elevated before HD due to impair its secretion through the kidney in urine (it increases as GFR decreases), chronic inflammation, endothelial dysfunction and subclinical coagulation activation. The level of D-dimer after HD is also elevated as a result of increase fibrinolytic activity due to activation of the coagulation cascade in HD and the use of anticoagulants during the HD.[23,28,29] Factor VIII activity increased before HD, that is part of a prothrombotic state seen in CKD, due to endothelial dysfunction, inflammatory responses, reduced clearance of procoagulant factors due to declining renal function and increased level of VWF which is protects FVIII from the degradation and stabilized it in the circulation. After hemodialysis factor VIII level increased because is not remove by dialysis, hemococentration, endothelial injury, and released from the activated platelet membrane due to its interaction with dialyser membrane.[23,24,30] The Von Willebrand factor level is elevated before HD, as result of endothelial cell injury by uremic toxins, inflammation, and oxidative stress associated with the condition. The renal function impairment reduces the clearance of VWF via urine, which leads to elevated its levels, the level of VWF Ag after HD elevated due to dialysis related inflammation which lead to endothelial activation and increase release of VWF, also the removal of ADAMTS13activity leads to increase level of circulating VWF.[23,24,31]

The mean values of PT, APTT, D-dimer, and FVIII levels after hemodialysis were significantly higher as compared to before HD. These results are in line with those of previous studies by Palvo et al.[23] the levels of fibrinogen, FVIII and VWF were significantly elevated in after HD with (P < 0.05), while the PT and APTT were significantly decreased after HD (P <0.05). Jessica et al.[24] reported significantly elevation of fibrinogen, FVIII and VWF Ag with (p <0.001), and Abdelrahman et al.[21] mentioned the PT, INR, APTT, fibrinogen and D-dimer were significantly increased after HD.

The analysis of blood urea and serum creatinine correlation with hemostatic parameters before hemodialysis non-significant correlation among patients, except serum creatinine had direct nearly significant correlation with fibrinogen (P value 0.055). There are several possible explanation for this result, fibrinogen is elevated in ESRD due to effect of uremia which cause chronic inflammation induced secretion of pro-inflammatory cytokines like interleukin 6 that increase production of fibrinogen from the liver, reduced its clearance via kidney endothelial dysfunction.[27]

The analysis of GFR correlation with hemostatic parameters before hemodialysis, it had an direct statically significant correlation with PT, INR with P value (0.046) and (0.027) respectively, these don't match those observed in study by Huang et al.[31] reported a significant inverse correlation with FVIII and VWF Ag. These data must be interpreted with caution because, in end stage renal disease, chronic uremia and dialysis cause chronic inflammation, endothelial dysfunction and coagulation factors deficiency, which lead to unexpected hemostatic parameter relationship.[32] The results of this study did not show any significant correlation of blood urea, serum creatinine and GFR with hemostatic parameters after hemodialysis.

The APTT had indirect significant correlation before HD with FVIII P value (0.000). There are several explanation for this results, factor VIII activity increased in ESED due to endothelium dysfunction and inflammation induced by uremic toxins as FVIII is a component of intrinsic coagulation pathway, leads to shortening time of APTT (measured the common and intrinsic coagulation pathway).[33] Also APTT had indirect non-significant correlation after the dialysis with FVIII. The data must be interpreted with caution because in hemodialysis dependent ESRD patients, there are multiple factors influence in coagulation system, dialysis related effect (heparin and shear stress), uremic toxins, endothial injury and chronic inflammation, that affect APTT and FVIII in independent way.[32,34] In addition in this study, the

APTT had direct non-significantly correlation with VWF Ag before the dialysis, is the same as Gadallah et al.[35] study. After hemodialysis the APTT had direct non-significantly correlation with VWF Ag, this because the coagulation system influence by many factors that affect hemostatic parameters independently.[32,34] The factor VIII had non-significant correlation with VWF Ag before and after HD, this is because of the effects of uremic toxins, endothelial injury, reduced clearance, inflammation, comorbidities and dialysis related shear stress affect VWF that leads to cleavage and loss large multimer, so the common correlation may be lost or become weak.[32,34,36] Hemodialysis accelerate the increase in hemostatic parameters by several mechanism, so it is not the ideal renal replacement therapy.[37]

CONCLUSION

In chronic kidney disease patients before hemodialysis, hemoglobin, hematocrit, red blood cells, and platelets were significantly lower compared to controls, while mean corpuscular volume was higher. Key findings include significant inverse correlations between hemoglobin, hematocrit, red blood cells, and blood urea. Activated partial thromboplastin time (aPTT) was prolonged in patients before and after hemodialysis compared to controls, alongside increased levels of prothrombin time, D-dimer, fibrinogen, factor VIII, and von Willebrand factor. Prothrombin time and INR showed direct correlations with glomerular filtration rate prior to dialysis, and a strong negative correlation existed between aPTT and factor VIII before dialysis.

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