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Original Research Article

Evaluation of Blood Coagulation Parameters in Chronic Kidney Diseases

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ABSTRACT

Patients with chronic kidney disease (CKD) are prone to haemorrhage and/or thrombi formation, suggesting abnormalities in haemostasis. The study aimed to investigate the impairment of coagulation factors in CKD patients. One hundred and twenty-three (123) CKD patients, who were attending Prince Hamza and Al-Karak public hospitals, and fifty (50) healthy subjects (control) were recruited for the study. CKD patients were subcategorized according to their GFR value into III B and IV groups. Ethical approval was obtained, and all participants consented to the study. Whole blood samples were collected from all the CKD patients and 50 control (healthy) subjects and tested for prothrombin time (PT), activated partial thromboplastin time (aPTT), and coagulation factors I (fibrinogen), II, V, VII, VIII, IX, X, XI, and anti-thrombin III (ATIII) on STA coagulation analyzer. The levels of proteins C, S, and von Willebrand factor (VWF) were measured using enzyme-linked immunosorbent assay (ELISA). The findings showed a significant prolonged PT and aPTT in CKD patients compared to the control (healthy) subjects, and the level of F-V and F-XI were significantly decreased, justifying the clinical manifestation of bleeding in CKD patients. However, factors VII, VIII, and IX were increased significantly in CKD patients. The findings from this study have demonstrated that CKD impairs the coagulation factors and leads to an increase in the time required for clot formation, suggesting a tendency of patients with CKD to have frequent bleeding episodes.

Keywords: Hemostatic abnormalities, Chronic kidney diseases, Prothrombin time, Activated partial thromboplastin time, von Willebrand factor.

Introduction

Hemostasis is the process where the circulatory system conserve blood in the fluid state within arteries and veins, and prevent blood loss upon injury.[1] It occurs in three stages: primary stage (the action of the blood vessels and platelets), secondary stage (the actions of the protein coagulation factors), and fibrinolysis.[2-4] Coagulation proteins are procoagulant proteins that can be categorized into three groups according to their structural and functional properties;[5] (i) The prothrombin group includes factors II (prothrombin), VII, IX, and X; these are vitamin K-dependent factors produced by the liver, and they contain GLA-domain (γ-carboxyglutamic acid-rich region) that are vital for Ca^{2+}-binding.[5] (ii) The fibrinogen group includes factors I (fibrinogen), V, VIII, and XIII, and (iii) Contact group includes XI, XII, Prekallikrein (PK), and high molecular weights kininogen (HK) proteins.[5] In addition to coagulation factors, there are Ca^{2+} (factor IV), an essential component for efficient coagulation complex formation, and the large glycoprotein von Willebrand factor (VWF), produced from platelets and blood vessels.[6, 7]

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In vitro, the coagulation cascade occurs in intrinsic and extrinsic pathways, which are converged in a third path called the common pathway to generate the fibrin clot[8-11] (Figure 1). The coagulation reactions are kept in balance by activators and inhibitors of clotting and fibrinolysis; Anti-thrombin III (AT III), protein C (PC), and protein S (PS) are naturally occurring protein inhibitors that are soluble in plasma.[12,13] AT III neutralizes thrombin, XIIa, XIa, IXa, and Xa proteins, while PC and its cofactor PS inhibit factors Va and VIIIa.[14-16] Kidney disease is a widespread pathological condition,[17] mostly due to the increased incidence of a secondary pathology such as hypertension, chronic inflammation, autoimmune diseases, diabetes, and chronic use of anti-inflammatory medications, which leads to progressive kidney damage and reduction in the glomerular *f*iltration rate (GFR).[17-21] Chronic kidney disease is an irreversible clinical syndrome due to deterioration of kidney function and/or structure.[22] Patient is diagnosed with CKD when GFR is below 60 mL/min/1.73 m^2 for at least three months,[18, 23] or more than 60 mL/min/1.73 m^2 if it is associated with renal injury indicators including albuminuria, haematuria, leukocyturia, and changes in renal imaging (Table 1).[22,24]

Patients with CKD demonstrate a high risk of cardiovascular diseases, anemia, bone disorders, and metabolic acidosis.[24-26] In CDK, there is a disruption in coagulation, which usually manifests as severe bleeding from gums, gingiva, genital mucosa, hemoptysis, telangiectasia, hemarthrosis, and petechiae or thrombosis.[1, 27-29] The present study evaluated the impairment of coagulation parameters among CKD patients (mainly stages III B and IV) by measuring blood levels of prothrombin (PT), Activated partial thromboplastin time (aPTT), factors I (fibrinogen), II, V, VII, VIII, IX, X, XI, anti-thrombin III, protein C, protein S (total), and von Willebrand factor (VWF).

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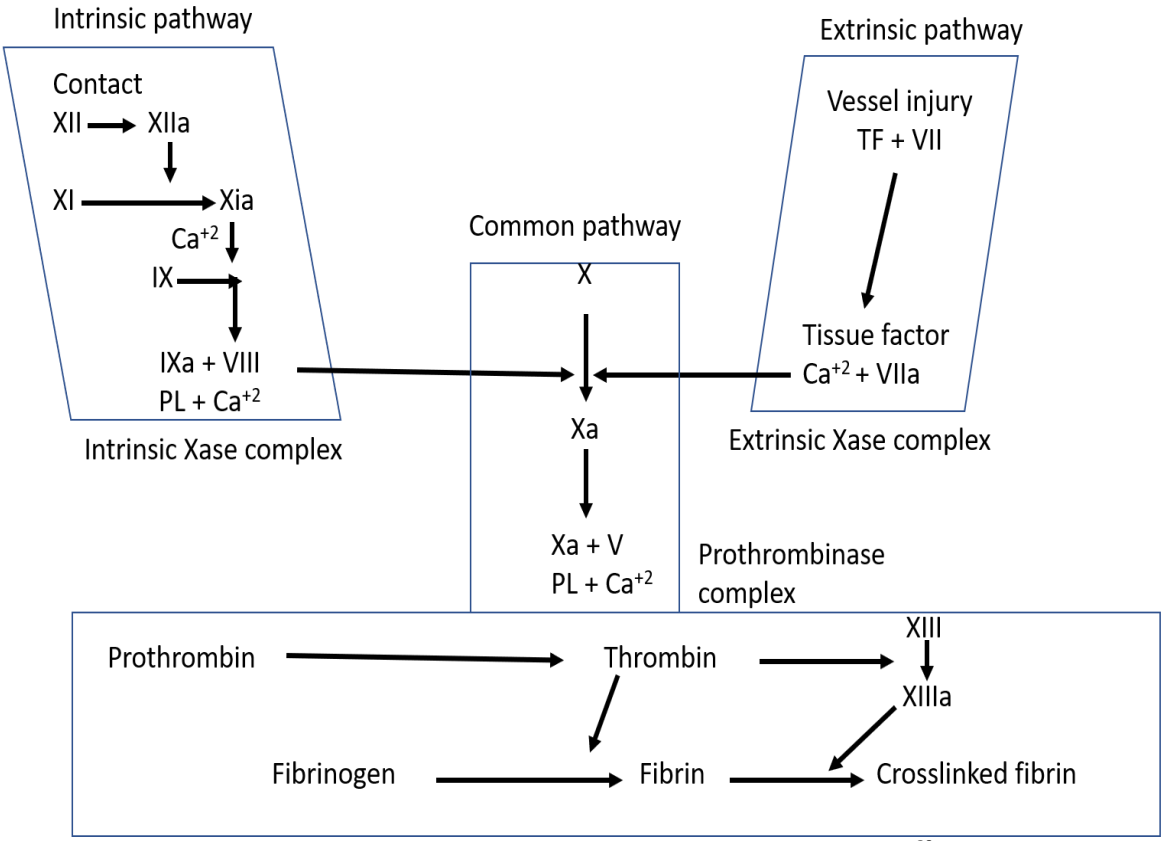

Figure 1: Schematic representation of the coagulation cascade.[28]
A simplified version of the coagulation cascade showing the cascade sequence of protein reactions. Boxes indicate complex formation. PL: platelet phospholipid, TF: tissue factor.

Table 1: CKD classification

Based on GFR value	
Stage	GFR (mL/min/1.73m^2)
I	>90
II	60-89
III A	45-59
III B	30-44
IV	15-29
V	<15
Based on Albuminuria value	
Stage	24-hour Albuminuria mg/24 h
A1	<30
A2	30-300
A3	>300

Materials and Methods

Materials
STA- NeoPTimal, STA-Liquid fibrinogen, STA- Deficient II, STA-Deficient V, STA-Deficient VII, STA-immunoef VIII, STA-Immunodef IX, STA- Deficient X, STA-Immunodef XI, and STA-Stachrom ATIII were purchased from Stago. Protein S (total) (CAT# ELK2722) and protein C (CAT# ELK2048) ELISA kits were purchased from ELK Biotechnology, China. The Human vWF ELISA kit (CAT# EH1064) was purchased from Finetest, China.

Study population
One hundred and twenty-three (123) CKD patients consisting of those with glomerulonephritis (n = 32), polycystic kidney disease (n = 19), and those with unknown cause of CDK (n = 72), who were attending Prince Hamza and Al-Karak public hospitals, and fifty (50) healthy subjects were recruited for the study. Patients with haematological and liver disorders were excluded from the study. CKD patients were subcategorized according to their GFR value into III B and IV groups, and their medical history and laboratory results were checked *(*Table 2*)*. The healthy participants (control group) were tested for kidney function, and full blood count to ensure they *were* healthy. All participants (patients with CKD and healthy subjects) agreed to sign off a consent participants form.

Ethical approval
Ethical approval for the study was obtained from the committee for research on humans at the Jordanian Ministry of Health, with approval number: 12104. The study was conducted according to the ministry's regulations.

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Table 2: Clinical characteristics of the study participants

Parameter	**Healthy individual (N = 50)** **Male (30, 60%)** **Female (N = 20, 40%)**	**Patients with CKD (N = 123)** **Male (N = 71, 57.7%)** **Female (N = 42.3%)**			
		Stage IIIB (N = 57)	Stage IV (N = 66)	All patients	P-value
Age: 1. Mean	1. 40 years	1. 49.6 years *P	1. 52.2 years *P	1. 51 years *P	<0.0001
2. SD	2. 4.4	2. 9.9	2. 8.9	2. 9.4	
3. Range	3. (32-48) years	3. (35-70) years	3. (35-68) years	3. (35-70) years	
Weight (Kg) ±SD	84.6 ± 3.5	76.8 ± 6.4 *P	75.2 ± 6.9 *P	75.9 ± 6.6 *P	<0.0001
Creatinine (µmol/L)	90	200 *P	220 *P	211 *P	<0.0001
eGFR (mL/min/1.73m^2)	82	31 *P	27 *P	28.6 *P	<0.0001
Haemoglobin (g/dL)	14.1	11.1	8.4	9.4	-
RBC count (10^{12}/L)	4.7	3.66	2.74	3.1	-
Haemodialysis (average per week)	No dialysis	57 (3 times)	66 (3 times)	123 (3 times)	-
CRP (mgl/dL) negative ≤5.0	N. A	40.1	28.7	34.4	-
Albumin g/dL Normal Range (3.4-4.8)	N. A	2.5	3.3	3.0	-
Uraemia Normal range (1.8-7.1mmol)	5.7	15.2	19.4	17.6	-
Albuminuria (mg/g)	N. A	36.4	39.8	37.8	-
Nutrition	Good	N. A	N. A	N. A	-
Associated disease.					-
Diabetes	0	1. 57	43	100	
Hypertension	0	57	63	120	
SLE	0	N.A	N.A	N.A	
Multiple myeloma	0	N.A	N.A	N.A	
Medications	No	Sodium bicarbonate, calcium carbonate, Alphacalcidol, Angioensin converting enzyme inhibitors.	Sodium bicarbonate, calcium carbonate, Alphacalcidol, Angioensin converting enzyme inhibitors.	Sodium bicarbonate, calcium carbonate, Alphacalcidol, Angioensin converting enzyme inhibitors.	-
Packed RBC transfusion (mean)	No	2 units after dialysis on irregular basis	2 units after dialysis on irregular basis	2 units after dialysis on irregular basis	-
Fresh frozen plasma (FFP) transfusion (mean)	No	6 units after dialysis on irregular basis	6 units after dialysis on irregular basis	6 units after dialysis on irregular basis	-
Kidney transplant	No	No	No	No	-

Stage IIIB: eGFR (30-44) ml/min/1.73m^2, stage IV: eGFR (15-29) ml/min/1.73m^2. N.A: data not available. *P <0.0001 vs control.

Blood sample collection

Whole blood samples were withdrawn in tubes containing sodium citrate (3.2%) anticoagulant from the 123 patients with CKD prior to undergoing hemodialysis, and the 50 healthy subjects. The tubes were centrifuged at 4000 rpm for 10 minutes at 4ºC; then plasma was collected and stored at -20ºC. The samples were analyzed in batches (about 20 samples per batch).

Standard coagulation assays

These include (i) PT test, which measures the time required for blood clotting (thromboplastin formation), (ii) aPTT test, which measures the time required for blood clotting in the presence of phospholipid, and (iii) fibrinogen test which is measured on the STA CompactMax3 coagulation analyzer.

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Special coagulation assays
These include II, V, VII, VIII, IX, X, XI, and anti-thrombin assays which were measured on the STA CompactMax3 coagulation analyzer.

Enzyme-linked immunosorbent assay (ELISA)
Sandwich enzyme immunoassay ELISA kits were used to measure the level of proteins C, S (total), and VWF.

Statistical analysis
Data were presented as mean ± standard error of mean (SEM) of three independent experiments. Data were analyzed by one-way analysis of variance (ANOVA) using the Graphpad prism software. P-value ≤ 0.05 was indicative of significant difference between means of the compared groups (CDK patients and healthy subjects).

Results and Discussion

Standard coagulation assay result
The standard coagulation assay revealed a significant increase in both PT (15.9 seconds) and aPTT (53.8 seconds) in the CKD patients compared to the control group ($P \leq 0.0001$, and $P \leq 0.0021$, respectively) (Figure 2A and 2B). This indicates that significantly longer time is needed for blood clot formation in CKD patients compared to the healthy subjects. However, there was no significant difference in the blood fibrinogen level between CKD patients and the healthy control group (Figure 2C). In the patient subgroups (III B and IV stages) it was evident that PT and aPTT were significantly prolonged in patients with stages III B and IV of CKD compared with the control group, but no significant changes were observed in fibrinogen level. Also, there were no significant differences in the PT, aPTT, and fibrinogen values between patients in the subgroups.

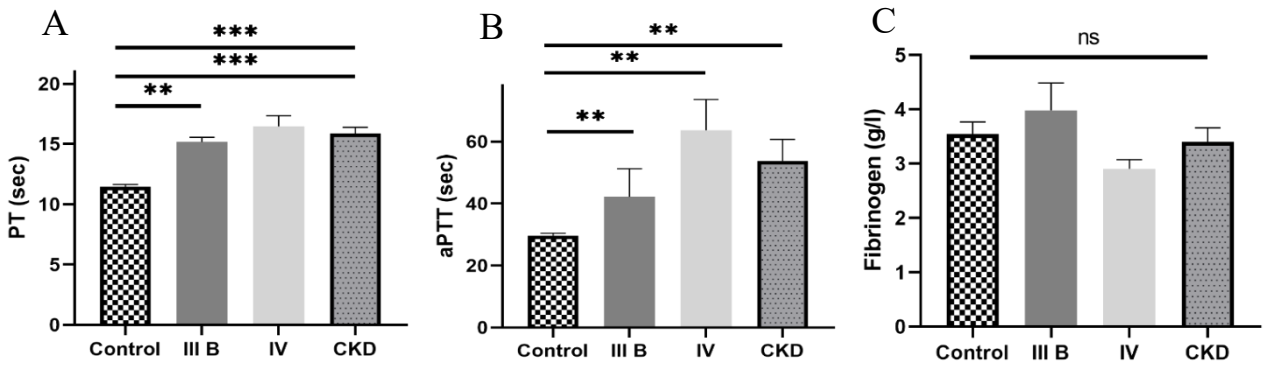

Figure 2: Results of the standard coagulation assay
(A): PT; prothrombin time, **(B):** aPTT; activated partial thromboplastin time, **(C):** Fibrinogen level. Control represents healthy subjects, III B represents patients with CKD stage III B, IV represents patients with CKD stage IV, CKD represents all patients with chronic kidney diseases (III B and IV stages). Each bar is a representative mean ± SEM from three independent experiments. ** and *** represent P-value ≤ 0.0021 and P-value ≤ 0.0001, respectively, while (ns) represents not significant.

Special coagulation assay result
To determine the effect of CKD on haemostatic proteins, the concentrations of clotting factors II, V, VII, VIII, IX, X, and XI, and ATIII were measured on a Stago coagulation analyzer. It was observed that the levels of VII, VIII, and IX were significantly increased in CKD patients, but surprisingly, the levels V, and XI were significantly decreased in CKD patients compared to the healthy control group. There was no significant difference in the concentrations of II, X proteins, and ATIII between the CKD patients and the healthy control groups (Figure 3).

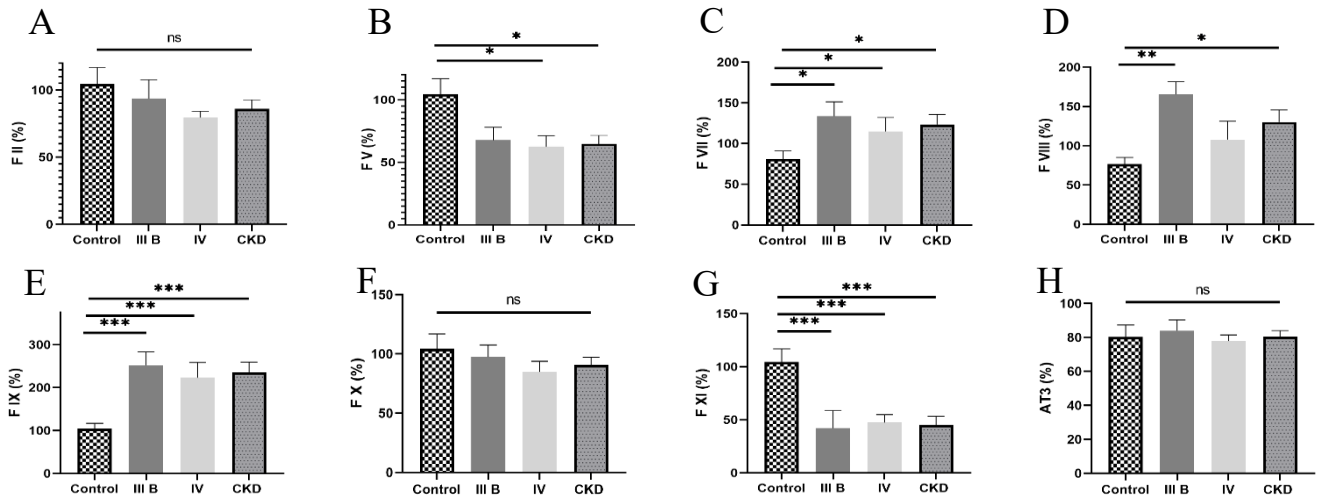

Figure 3: Results of the special coagulation assay
(A): Factor II (prothrombin) level, **(B):** factor V level, **(C):** factor VII level, **(D):** factor VIII level, **(E):** factor IX level, **(F):** factor X level, **(G):** factor XI level, **(H):** anti-thrombin level. Control represents healthy subjects, III B represents patients with CKD stage III B, IV represents patients with CKD stage IV, CKD represent all patients with chronic kidney diseases (III B and IV stages). Each bar is a representative mean ± SEM from three independent experiments. *, ** and *** represent P-value ≤ 0.05, P-value ≤ 0.0021 and P-value ≤ 0.0001, respectively, while (ns) represents not significant.

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The same observation occurred when the patient's subgroup (III B and IV) were compared with the control group, except that there was no significant difference in the level of factors VII and VIII between CKD patients at stage IV and the control group, while there was no significant difference in the level of factor V between patients with CKD stage III B and the control group. Subgroups of patients were also compared, and there was no significant difference between them in all the blood clotting factors tested.

Levels of Proteins C, S (total), and VWF in CKD patients

Sandwich enzyme immunoassay was used to measure proteins C, S (total), and VWF, where a 96-well plate was pre-coated with antibodies specific to protein C, protein S, or VWF. The results showed that there was no significant difference in the levels of proteins C, S, and VWF between patients with CKD and healthy subjects, and between subgroup of patients with CKD (Figure 4). The results contradicted previous findings by Jalal *et al*. who reported that both protein S and VWF were increased in patient with chronic kidney diseases.[1]

Haemostasis is a delicate balance of primary and secondary haemostatic action, their inhibitors, and the fibrinolytic system.[3] Several diseases are associated with an imbalance in haemostasis through excessive bleeding, such as haemophilia (A and B) and liver diseases,[30, 31] blood thrombosis like factor V Leiden, and sepsis,[32,33] or both (bleeding and thrombosis) like disseminated intravascular coagulation.[34]

Anaemia is usually associated with chronic kidney diseases, because it is known that the erythropoietin hormone, which stimulates the bone marrow to synthesize red blood cells, is produced by the kidneys.[35] However, coagulation impairment and the tendency for bleeding and/or thrombosis in patients with renal insufficiency is still unclear because of conflicting results from previous studies, which demonstrated that CKD patients are prone to bleeding episodes due to low platelet and clotting factors resulting from disorders of coagulation regulatory factors.[1,27,28] This is the first comprehensive evaluation of coagulation changes in CKD patients through measurement of PT, aPTT levels, and the levels of proteins of the coagulation cascade in extrinsic pathway (VII), intrinsic pathway (IX, and XI), common pathway (X, and V), prothrombin (II), fibrinogen (I)), and VWF. Also, the levels of proteins C, S (total), and anti-thrombin III were measured. Samples were collected from patients before haemodialysis to ensure that the coagulation factors were not compensated by plasma exchange or transfusion coinciding with haemodialysis.

The present findings is consistent with previous findings, which showed that urea accumulation in the blood of patients with CKD has a deteriorated effect on coagulation, resulting in a significantly prolonged PT and aPTT, which reflect the failure of the extrinsic, intrinsic, and/ or common pathways in clot formation, and the tendency for bleeding in the patients before hemodialysis.[36, 37]

It was also observed that factors V and XI were significantly reduced in patients with CKD except for patients at stage III B who showed no significant change in the level of factor V, which is consistent with the findings of Pavlou *et al*. with respect to factor V, but contradicts the findings with respect to factor XI.[36] It is known that F-V and F-XI are crucial in the coagulation cascade; F-V is a cofactor for activated F-X, which both are a component of a prothrombinase complex in addition to Ca^{2+} and phospholipids; this complex activates prothrombin to thrombin.[38] F-V is activated primarily by thrombin and F-Xa, and inhibited by the activated protein C and its cofactor protein S.[39] The decreased level of these factors suggests the tendency of patients with chronic kidney diseases to bleed, which is consistent with the findings from the present study with respect to prolonged PT and aPTT in CKD patients. Similarly, previous studies have shown that factors VII and VIII (except for stage IV patients) are significantly increased in CKD patients. [40, 41] The same is observed for F-IX, which is significantly increased in patients with CKD.

With respect to blood coagulation inhibitors, no significant changes were observed in proteins C, S (total), and anti-thrombin III in CKD patients compared with the healthy group, suggesting that patients with CKD experience severe bleeding because of coagulation factors deficiency and not because of increased level of coagulation factors inhibitors. In contrast to the results of the present study, it has been shown that the levels of fibrinogen, F-XII, VWF, and activated protein C were significantly increased in CKD patients.[1, 40]

It is important to state that the present evaluation of coagulation factors and inhibitors in CKD patients was limited because the patients received fresh frozen plasma (FFP) on an irregular basis, as indicated in Table 2. This may explain the increase in the levels of fibrinogen (not significant) and VII, VII, and IX (significant) in CKD patients compared to the healthy control group.

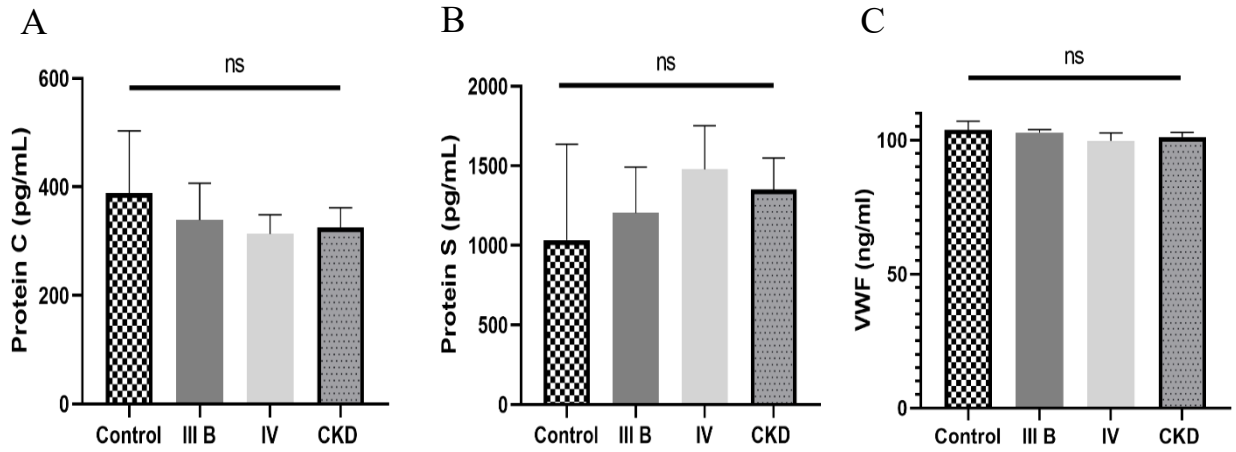

Figure 4: Proteins C and S, and VWF levels

(A): Protein C level, (B): Protein S total level, (C): Von Willibrand factor (VWF) level. Control represents healthy people, III B represents patients with CKD stage III B, IV represents patients with CKD stage IV, CKD represent all patients with chronic kidney diseases (III B and IV stages). Each bar is a representative mean ± SEM from three independent experiments (technical number: 3 wells per plate). ns represents not significant

Conclusion

The findings from the present study have demonstrated a significant increase in the concentrations of blood clotting factors VII, VIII, and IX, and a significant reduction in factors V, and XI in CKD patients. In addition, the results indicate an increased tendency to bleed in patients with CKD which is clearly attributed to the prolonged PT and aPTT in these patients.

Conflicts of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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