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Review Article

Impact Of Type 2 Diabetes Mellitus On Activated Partial Thromboplastin Time and Serum Fibrinogen In Non-dialysis Chronic Kidney Disease Patients

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ABSTRACT

Background: due to abnormalities in coagulation and hypo-fibrinolysis, diabetes mellitus is linked to an increased risk of thrombotic complications. In patients with chronic kidney disease (CKD), pro- and anti-hemostatic factors are disrupted, leading to both bleeding and thrombotic complications. However, few studies have shown how diabetes mellitus affects serum fibrinogen levels and APTT in non-dialysis CKD patients.

Aim of the work: To investigate impact of type 2 DM on APTT and serum fibrinogen in Non-dialysis CKD patients.

Patients and methods: 150 patients classified into 3 groups each group included 50 patients, group with DM only patients, group with CKD only patients and group with CKD and DM patients , demographic data, APTT, serum fibrinogen , HbA1c and eGFR were done for all patients.

Results: Combining DM with CKD led to a significant increase in serum fibrinogen level ($p<0.0001$) and a reduction in APTT ($p<0.0001$). Serum fibrinogen also showed a positive correlation with HbA1c and eGFR ($p<0.0001$, $r = 0.8$) ($P <0.002$, $r = 0.26$) and a negative correlation ($P<0.0001$, $r = -0.66$) ($P< 0.0001$, $r = -0.50$) with HbA1c and eGFR.

Conclusion: Serum fibrinogen, APTT, and glycemic state should all be closely watched in non-dialysis CKD patients. This can help lower the risk of thrombosis in the future.

Keywords: Type 2 diabetes mellitus; APTT; Fibrinogen; Non-dialysis chronic kidney disease.

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Introduction

Individuals with diabetes mellitus (DM) who have metabolic abnormalities that throw off the natural equilibrium between fibrinolysis and coagulation, resulting in a prothrombotic state marked by hypo-fibrinolysis, coagulation disorders, and platelet hy-persensitivity Most of the time, hyperglycemia can directly affect vascular endothelium's susceptibility by altering its glycocalyx layers; as a result, this process improves platelet-endothelial cell adhesion and releases coagulation factors, which in turn causes the formation of occlusivethrombus . [(1)]

thrombotic problems in chronic kidney disease diabetes mellitus, hyperglycemia and insulin resis-tance can alter and up-regulate the coagulation pro-tein gene expression pathway by potentially increa-sing oxidative stress production. Consequently, pro-thrombotic coagulation factors such fibrinogen, tiss-ue factor and factor VII, plasminogen activator inh-ibitor-1, and other pathogenic pro-inflammatory cy-tokines are synthesized at higher rates during this phase. [(2)]

The imbalance between pro- and anti-hemostatic factors is the primary cause of both bleeding and (CKD), which results in high rates of morbidity

and mortality.[3,4,5] Blood viscosity, thrombogenesis, bl-ood rheology, and platelet aggregation are all infl-uenced by plasma fibrinogen levels.

Standard coagulation screening tests, like blood fibrinogen level and activated partial thromboplastin time (aPTT), are still crucial basic examinations in clinical laboratories, even if more complex coag-ulation diagnostic tests are being developed nowa-days.

Reduced aPTT readings may indicate a hypercoagulable state, which may be linked to a higher risk of thrombosis and unfavorable cardiovascular events. [6,7] A build-up of circulating activated coagul-ation components in plasma brought on by increase-ed coagulation activation in vivo may be the cause of shortened aPTT. [6,8] As a result, in individuals with diabetes mellitus, aPTT can be used to eva-luate the risk of thromboembolic consequences. [6,9]

PATIENTS AND METHODS

We performed a cross sectional study on 150 Patients who were aged 18 to 75 years old and we clas-sified study participants into 3 groups:

a) 50 Non-dialysis CKD patients without diabetes mellitus
b) 50 Diabetic patients without detectable CKD
c) 50 Non-dialysis CKD Patients with diabetes mellitus

Exclusion criteria :

- History of malignancy
- Chronic liver illness;

History of known inherited bleeding disorders; • Infectious diseases (hepatitis B, hepatitis C, and human immunodeficiency virus).

- Alcoholics, habitual tobacco chewers, and smokers
- CKD patients receiving hemodialysis

Pregnancy or lactation

Use of anticoagulant or antiplatelet medications and oral contraceptives

patients were subjected to :

- History taking and physical examination
- A structured using questionnaire were collected to detect Socio-demographic characteristics and clinical information of study participants
- Kidney Disease Improving Global Outcomes (KDIGO) defines chronic kidney disease (CKD) as "Abnormalities of kidney structure or function, present for >3 months, with implications for health" is the definition of chronic kidney disease (CKD). One of two requirements must be met, either by means of documentation or inference, for >3 months to be considered: either GFR <60 ml/min/1.73 m2 or kidney damage markers, such as albuminuria. [10]
- The Epidemiology Collaboration equation (eGFR) was utilized to compute the glomerular filtration rate (GFR). [11]
- In accordance with Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations, the CKD patients were divided into 4 groups based on GFR. [10]
- GFR >90 mL/min/1.73 m2+ proteinuria is the definition of stage 1.
- GFR 89–60 mL/min/1.73 m2 is the definition of Stage 2; GFR 59–30 mL/min/1.73 m2 is the definition of Stage 3; and GFR 29–15 mL/min/1.73 m2 is the definition of Stage 4.
- If one or more of the following conditions are satisfied, DM will be diagnosed through laboratory testing:
- A random glucose level > 11.1 mmol/l (200 mg/dl) or a fasting plasma glucose level ≥7.0 mmol/l (126 mg/dl) or a two-hour plasma glucose level ≥11.1 mmol/l (200 mg/dl) after a 75 g oral glucose load, or a HbA1c ≥ 48 mmol/l (equal to 6.5%). [12]
- We classified diabetic patients into 2 groups according the type of anti-diabetic treatment received
- Patient group receiving insulin therapy
- Patient group receiving oral hypoglycemics
- A normal spot urine albumin-creatinine ratio was determined to be less than 20 mg/g for men and less than 30 mg/g for women. When the spot urine albumin–creatinine ratio is 20–200 mg/g in men and 30–300 mg/g in women, it is referred to as microalbuminuria. [10]
- Patients with a HbA1c test result of less than 5.7% were categorized as normal, or in the non-diabetic range; those with a result of 5.7% to 6.4% were classified as prediabetics; and those with a result of 6.5% or above were labeled as diabetic patients. [12]

- Serum fibrinogen reference ranges were : 200-400 mg/dL or 2-4 g/L for Adults. [13]
- APTT was determined using the HUMACLOTJUNIOR coagulometer. [13]
- Imaging : Abdominal Ultrasound study was done for all studied patients

The study protocol was approved by scientific and ethical committees at Sohag Faculty of Medicine and an informed written consent was obtained from all participants.

Statistical analysis

STATA version 17.0 (Stata Statistical Software: Release 17.0 College Station, TX: Stata Corp LP.) was used to analyze the data. The distribution of the various variables was ascertained using the Shapiro-Wilk normality test. The measures used to express quantitative data were mean, standard deviation, median, and range. ANOVA was used to compare the means of three groups or more for analyzing the data, and the student t-test was used to compare the means of two groups. The Mann-Whitney test was used to compare two groups and the Kruskal Wallis test was used to compare three or more groups when the data were not normally distributed.

The Chi square test or Fisher exact tests were used to compare the numerical and percentage forms of the qualitative data. The Spearman correlation test was used for correlation analysis. The identification of variables influencing platelet indices and coagulation profile was also accomplished by multivariate linear regression analyses. If the P value was less than 0.05, it was deemed significant.

RESULTS

Table (1): Demographic and clinical feature of studied population

Variable	CKD N=50	DM N=50	CKD with DM N=50	P value
Age/years				
Mean ± SD	49.74±15.92	51.7±8.25	52±6.60	0.43
Median (range)	48 (18:80)	49.5 (39:70)	53.5 (38:67)	
P1=0.36, P2=0.26, P3=0.47				
Gender				
Female	25 (50.00%)	28 (56.00%)	17 (34.00%)	0.07
Male	25 (50.00%)	22 (44.00%)	33 (66.00%)	
P1=0.55, P2=0.11, P3=0.03				
BMI				
Mean ± SD	27.74±3.74	32.64±3.76	31.56±3.24	<0.0001
Median (range)	28 (22:37)	33 (23:40)	32 (25:38)	
P1<0.0001, P2<0.0001, P3=0.40				
Hypertension				
No	20 (40.00%)	29 (58.00%)	18 (36.00%)	0.06
Yes	30 (60.00%)	21 (42.00%)	32 (64.00%)	
P1=0.07, P2=0.68, P3=0.03				
Dyslipidemia				
No	34 (68.00%)	28 (56.00%)	28 (56.00%)	0.37
Yes	16 (32.00%)	22 (44.00%)	22 (44.00%)	
P1=0.22, P2=0.22, P3=1.00				

CKD= chronic kidney disease, DM= diabetes mellitus, BMI= body mass index

P value compared the three groups. P1 compared CKD & DM, P2 compared CKD & CKD with DM and P3 compared DM & CKD with DM.

Table (2): Coagulation profile of studied population

Variable	CKD N=50	DM N=50	CKD with DM N=50	P value
APTT				
Mean ± SD	38.08±2.28	30.5±1.62	32.44±1.96	<0.0001
Median (range)	38 (33:44)	30 (27:33)	33 (29:35)	
P1<0.0001, P2<0.0001, P3<0.0001				
Fibrinogen				
Mean ± SD	278.24±49.73	434.42±40.43	427.1±37.49	<0.0001
Median (range)	288 (180:346)	428.5 (345:520)	415.5 (378:510)	
P1<0.0001, P2<0.0001, P3=1.00				
Fibrinogen				
<400	50 (100%)	13 (26.00%)	20 (40.00%)	<0.0001
>400	0	37 (74.00%)	30 (60.00%)	
P1<0.0001, P2<0.0001, P3=0.14				

CKD= chronic kidney disease, DM= diabetes mellitus, APTT= activated partial thromboplastin time
P value compared the three groups. P1 compared CKD & DM, P2 compared CKD & CKD with DM and P3 compared DM & CKD with DM.

Table (3): Relation between stages of CKD and Coagulation profile

Variable		Group	Stage 2	Stage 3	Stage 4	P value for trend
APTT		**CKD**	36.63±1.69 36.5 (34:39)	37.44±1.20 38 (35:39)	39.04±2.68 39 (33:44)	0.003
		CKD with DM	33.2±1.10 33 (32:35)	32.23±1.89 32 (29:35)	32.43±2.13 33 (29:35)	0.66
		Both groups	35.31±2.25 35 (32:39)	34.91±3.06 35 (29:39)	35.48±4.09 35 (29:44)	0.66
P value compared 2 group			0.002	<0.0001	<0.0001	
Fibrinogen		**CKD**	271.25±57.78 285 (186:346)	265.94±50.06 282.5 (180:342)	289.94±46.11 298 (185:343)	0.20
		CKD with DM	418.4±34.53 400 (390:473)	408.24±25.80 399 (378:478)	440.11±39.58 427.5 (388:510)	0.02
		Both groups	327.85±88.86 318 (186:473)	335.06±82.30 342 (180:478)	370.73±86.68 393 (185:510)	0.04
P value compared 2 group			0.0003	<0.0001	<0.0001	
Fibrinogen	**≤400** **>400**	**CKD**	8 (100%) 0	18 (100%) 0	24 (100%) 0	
	≤400 **>400**	**CKD with DM**	3 (60.00%) 2 (40.00%)	10 (58.82%) 7 (41.18%)	7 (25.00%) 21 (75.00%)	0.03
	≤400 **>400**	**Both groups**	11 (84.62%) 2 (15.38%)	28 (80.00%) 7 (20.00%)	31 (59.62%) 21 (40.38%)	0.6
P value compared 2 group			0.05	0.002	<0.0001	

CKD= chronic kidney disease, DM= diabetes mellitus, PT= prothrombin time, PC= prothrombin concentration, INR= international normalized ratio, APTT= activated partial thromboplastin time

Table (4): Correlation between HbA1C with platelet indices, coagulation profile and other lab findings

Variable	CKD		DM		CKD with DM		All patients	
	R	p	r	p	R	P	r	P
APTT	0.25	0.08	-0.02	0.91	-0.15	0.31	-0.66	**<0.0001**
Fibrinogen	0.18	0.22	0.49	**0.0003**	0.35	0.01	0.80	**<0.0001**

r -- Spearman's correlation co-efficient, P – Value
CKD= chronic kidney disease, DM= diabetes mellitus,

Table (5): Correlation between eGFR with platelet indices, coagulation profile and other lab findings

Variable	CKD		DM		CKD with DM		All patients	
	r	p	R	p	R	P	r	P
APTT	-0.31	**0.03**	-0.11	0.45	0.19	0.19	-0.50	**<0.0001**
Fibrinogen	-0.24	0.10	-0.25	0.08	-0.46	**0.001**	0.26	**0.002**

r -- Spearman's correlation co-efficient, P – Value
CKD= chronic kidney disease, DM= diabetes mellitus,

Table (6): Multivariate regression analysis of parameters affecting Fibrinogen.

Variable	Regression co-efficient (95% CI)	P value
Age	0.33 (-0.41:1.06)	0.38
Male gender	3.34 (-10.20:16.89)	0.63
Hypertension	3.18 (-12.34:18.70)	0.69
Dyslipidemia	-7.69 (-22.69:7.30)	0.31
BMI	3.24 (1.12:5.35)	0.003
HbA1C	8.29 (2.84:13.74)	0.003
eGFR	-0.44 (-1.15:0.27)	0.22
DM vs. CKD	134.83 (73.94:195.71)	<0.0001
CKD with DM vs. CKD	103.10 (78.75:127.55)	<0.0001

CKD= chronic kidney disease, DM= diabetes mellitus, eGFR= glomerular filtration rate, BMI= body mass index

Table (7): Multivariate regression analysis of parameters affecting APTT.

Variable	Regression co-efficient (95% CI)	P value
Age	0.02 (-0.02:0.05)	0.40
Male gender	-0.48 (-1.17:0.22)	0.18
Hypertension	0.32 (-0.48:1.12)	0.43
Dyslipidemia	-0.27 (-1.04:0.51)	0.50
BMI	-0.04 (-0.15:0.07)	0.52
HbA1C	-0.05 (-0.33:0.23)	0.72
eGFR	-0.02 (-0.06:0.02)	0.25
DM vs. CKD	-5.75 (-8.88:-2.61)	**<0.0001**
CKD with DM vs. CKD	-5.29 (-6.54:-4.03)	**<0.0001**

CKD= chronic kidney disease, DM= diabetes mellitus, eGFR= glomerular filtration rate, BMI= body mass index

Discussion

Few studies have looked at how diabetes affects CKD patients' coagulation profiles without using hemodialysis.

Cardiovascular issues are linked to both conventional (such as diabetes mellitus, hypertension, or age) and nontraditional (such as albuminuria, oxidative stress, or inflammation), risk factors for CKD that mostly stem from the disease itself. In all phases of CKD and DM, there is an elevated risk of cardiovascular and thromboembolic events as well.

Additionally, we discovered that Activated Partial Thromboplastin Time (APTT) was shorter in patients with diabetes mellitus (DM) with or without CKD than in patients with CKD alone. This suggested the impact of DM in combination with CKD and that APTT is negatively correlated with HBA1C. These findings were consistent with Pan L et al., **(14)**, who discovered that APTT is shortened in diabetic patients with or without nephropathy

Additionally, Sapokata B et al., (16) indicated that diabetes patients with and without nephropathy had significantly shorter APTTs than non-diabetics .

Furthermore, we discovered that APTT is unaffected by CKD stage.

Additionally, we discovered that the fibrinogen level was positively connected with and influenced by HBA1C and BMI values, and that it was considerably higher in stage 4 CKD compared to previous stages in CKD patients with DM compared to CKD patients without DM.

That was In line with Zhao Y et al., **(15)** who found that the level of serum fibrinogen was significantly higher in patients with diabetic nephropathy compared to those without the condition, and who proposed that serum fibrinogen is a strong predictor of the occurrence of micro-vascular complications in diabetic patients, we found that the level of serum fibrinogen was significantly higher in diabetic patients with CKD compared to CKD only patients. It was also higher in diabetic patients who received oral hypoglycemic treatment compared to those who received insulin treatment.

This is also in line with the findings of Le D. S. et al, who discovered a statistically significant increase in serum fibrinogen concentration in patients with diabetic nephropathy when compared to diabetics without complications. They also proposed a link between elevated plasma fibrinogen concentration and diabetic microvascular complications, particularly nephropathy. This could provide light on the biological relationship between nephropathy and CVD. (17)

Conclusion

Our research led us to the conclusion that patients with CKD who are diabetic and have poor glycemic control have significant effects on their APTT and serum fibrinogen levels. Additionally, patients with CKD who are diabetics also have large increases in their serum fibrinogen levels .

Therefore, all CKD patients with DM must have their APTT and blood fibrinogen evaluated in order to determine their risk of thrombosis, forecast long-term cardiovascular system issues, and identify the most effective preventive strategies.

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